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THE RELATION BETWEEN NEUROSIS AND PSYCHOSIS

AN ANALYSIS OF SYMPTOMS AND PAST HISTORY OF
819 PSYCHOTICS AND NEUROTICS

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1. INTRODUCTION

WHILE it is usual among psychiatrists to express dissatisfaction with psychiatric classification and its problems it is by no means unusual for their psychological colleagues to advocate factor analysis as an effective technique for resolving such problems. For example, Burt (1954) describes factor analysis as "essentially a statistical device for securing the best available scheme of classification". Yet the problems and the device tend to remain apart, the former becoming intensified, the latter undergoing continued improvements. Twenty-five years ago T. V. Moore (1930) demonstrated that the application of factor analysis to the study of psychiatric disorders was feasible, and more recent work, especially that of Eysenck (e.g. 1947) has impressively shown its fruitfulness. That some clinicians remain sceptical of the claims made for these techniques is, in part, due to the infrequency with which factorial studies bearing on psychiatry have been pursued far enough for their implications to be tested and the findings integrated with those established by other scientific methods. This deficiency may be attributable to the fact that large scale programme research (Eysenck, 1953) is an almost essential condition, if this is to be achieved.

This study forms part of a research on psychiatric classification. A factor analysis of data relating to functional psychiatric disorders will be described here. Subsequently the results will be linked to certain clinical and psychological findings.

The starting point of the investigation is the Item Sheet of the London University Institute of Psychiatry used at the Bethlem Royal and Maudsley Hospitals. Since 1949 information about numerous aspects of each in-patient's illness has been recorded on Item Sheets and the data transferred to punched cards. Although intended for use chiefly in conjunction with case notes as an index, or for purposes such as ascertaining the incidence of various symptoms in a particular group of patients, a study of some of the large amount of information now accumulated with the Item Sheets themselves should prove a valuable aid in unravelling the complex interrelationships of the variables.

It is rare for a psychiatric institution to keep comprehensive records of this nature, which may be of great value in research. A record of the objective facts to which reference can be made provides a means of improving the reliability of psychiatric diagnosis. As the data relate both to psychotic and to neurotic patients, there is an opportunity of studying the relations between these two groups. Previous factor analytical studies have been concerned with either one or the other of these groups. The factor analytical study of the forerunner of the present Item Sheet, used at the Mill Hill Emergency Hospital, which had no data about psychotic patients, yielded the factors identified as Neuroticism and Introversion-Extraversion (Eysenck, 1944). These have since been amply confirmed in the programme of intensive research on these factors under Professor Eysenck's direction (1952, 1953).

2. OBJECTS OF STUDY

The principal aim of this study is to determine, by means of multiple factor analysis, the main independent factors (or dimensions) involved in the inter-correlations between certain variables in the Item Sheet.

The variables were selected to cover as comprehensively as possible the main symptoms and details from the past history of patients having non-organic psychiatric disorders.

It is hoped that this research will assist in locating some of the regions of disagreement which result in the present diagnostic chaos, as well as providing a link between the objective behavioural tests of the psychologist and current psychiatric practice. These applications and extensions will be amplified later.

Some of the possible causes of the present diagnostic difficulties should be mentioned. One such difficulty appears to arise because of the process of diagnosis still commonly being regarded as assigning a patient to a category, rather than locating his position relative to other patients in terms of various independent "*dimensions*". With further knowledge of the latter it should become possible to resolve the problems of the relationships of the various disorders, such as the extent to which "one type of psychiatric disorder changes into another". This assumption (according to Nolan Lewis (1949)) "does violence to established biological laws", the majority of such apparent changes being explained as occurring "not because of insufficient observation of symptoms but because of failure to interpret the diagnostic significance of the symptoms", (N. Lewis and Z. Piotrowsky, 1954). This may be taken as supporting the need for an objective and preferably quantitative technique for assessing symptoms in relation to all the other features. It also implies the need for improving the present system of diagnosis in which the relative importance attached to the items (the mingling of which in the mind of the clinician culminates in the diagnosis), is unknown and arbitrary. The present study should assist in clarifying some of these ambiguities and in demonstrating the relationship of "psychoticism" to the better established dimension of "neuroticism", although it is not possible here to formulate precise hypotheses from which "*direct*" rather than "*relational*" deductions (Eysenck, 1953, p. 28) can be made.

3. SOME LIMITATIONS OF THE STUDY

A variety of criticisms of the use of the Item Sheet data for a study of this kind have been made. Although inspection of the results is enough to refute these pessimistic forecasts, some of the difficulties involved in the use of the Item Sheet will be mentioned which may be of assistance if similar factorial studies are undertaken.

(1) In the first place the symptoms checked represent all that the patient has exhibited while in hospital and cannot therefore be regarded as a cross-section of his behaviour at a given moment. If this would appear to militate against valid deductions being made from the data, it is suggested that behaviour only takes place in time, e.g. "insomnia" requires at least one night to become manifest. The choice of interval during which the symptoms are studied is, however, of some importance, and this cannot be ascertained from the Item Sheets on which the length of stay in hospital is not recorded. The possibility that the changes in the patient's state during a long stay in hospital might obscure the pattern of symptoms is unlikely because:

(a) Only 185 of the 700 patients, included in the study of symptom incidence (Table Ib) had a "varied symptomatology in hospital".

(b) It is probable that many symptoms which appear successively in some patients may appear concurrently in others.

(2) The symptoms included in the Item Sheet are not adequately representative of all the major diagnostic categories, e.g. conversion hysteria is not clearly represented, there are few neurotic symptoms in the part of the Item Sheet dealing with the course of the illness in hospital, and manic symptoms (e.g. "flight of ideas", grandiose delusions and distractibility) are few.

(3) Some symptoms are combined with their opposites, which make the items unsuitable for inclusion, e.g. "Abnormalities of Speech: Quantity (mute, garrulous, etc.)". In other instances symptoms usually regarded as associated with rather different disorders are combined, e.g. "Inappropriate Mood" includes "belle indifférence" and incongruity of affect, and similarly indifference to symptoms is included with denial of symptoms.

(4) Few of the terms are defined, and some (e.g. "delusion of bodily change or disorder") may be differently interpreted by different psychiatrists.

(5) The section on "Previous Personality" presents difficulties both in relating the terms to the patient's behaviour and in analysis.

(6) The reliability of the data is unknown, but could possibly be assessed by comparing the Item Sheets of patients discharged and readmitted within a short interval.

(7) The extent of the various systematic errors of rating is unknown (e.g. halo effect and logical errors, differences in rating ability, etc.).

To conclude this section some of the merits of using the Item Sheet data should be mentioned. The first is that the psychiatric data embodied in them are not only vast in amount but fairly comprehensive and in a form which facilitates analysis (the range of possible items being the same for all patients and conveniently coded on punched cards). There is another major advantage, namely the probable absence of any consistent bias of the kind which would result if only one psychiatrist (or even a group of psychiatrists united by a common outlook and agreeing with each other) were responsible for collecting and filling in the information.

4. HISTORICAL

This section deals first with the recent work which has been done in the realm of psychiatry using factor analytical techniques. Only literature too recent for inclusion in the comprehensive reviews by Eysenck (1944, 1947, 1953) will be described in the first part and in what follows no attempt will be made to elucidate the vicissitudes of the history of the use of the terms "neurosis" and "psychosis".

In a recent study the now 25-year-old data of T. V. Moore (1930) were

re-analysed by Degan (1952). Thurstone (1934), had found that five orthogonal factors were enough to account for the (recomputed) correlations. Degan re-analysed the correlations between 32 of the symptoms and obtained nine factors: using Thurstone's methods he proceeded to oblique simple structure and the extraction of second order factors which he rotated to an oblique solution, but which were not "viewed with any confidence". The chief interest of the study is, perhaps, the illustration of how some of the current psychiatric groupings, such as mania, may be demonstrated in the second order analysis as a combination of two functionally unitary first order factors. The chief limitations of this study, besides the absence of any fresh data, are:

- (1) the large number of factors derived from the tetrachoric correlations, N being only 367,
- (2) the absence of neurotics from the population,
- (3) the lack of information concerning the position of the patients in terms of the factors,
- (4) the exclusion of any details other than symptoms, e.g. of past history.

Other recent studies, of which full details are not yet available are those by O'Connor (1952) and by Kline and Gerard (1953) who are engaged in a statistical study of the attributes of 1,000 patients admitted to a mental hospital. The parts of the Veterans Administration Research using the Multidimensional Patient Rating Scale which have already appeared (Lorr and Jenkins *et al.*, 1953, 1953a, 1954) suggest that it will be one of the largest and most comprehensive factor analytical studies of psychiatric symptoms yet carried out. A somewhat similar research has been described by Wittenborn and his colleagues in a series of articles summarized in "Symptom Correlates for Descriptive Diagnosis" (1953). Neither of these two important researches can be adequately assessed until full details become available.

Wittenborn developed a 55 item 4-point rating scale which was used independently in two psychiatric hospitals, the separate factor analyses yielding similar results. Nine orthogonal factors were obtained, but as it would be misleading merely to list the labels assigned to them and their description would necessarily be lengthy, the following will be confined to indicating briefly the wide scope of the 17 articles dealing with them in their various aspects.

The principal aim was to develop a means of arriving at a "Quantified descriptive multiple psychiatric diagnosis", for which purpose a "standardized cluster score" on the 9 factors is determined for each patient. These scores have been correlated with psychiatric diagnosis (1953), tests such as the Rorschach (1951a) and the Wechsler-Bellevue subtests (1951b), an occupational therapy rating scale (1951a) and also with biographical items (1951d). Another application of these cluster scores has been the demonstration of the symptomatic heterogeneity (in part due to sex differences) of patients assigned to the same diagnostic category, the differentiation of patients by this means being similar to the "typing" of the same patients using the method of correlation of persons ("P-analysis") (Wittenborn, 1952a and 1952b).

These studies, while showing the merits and potentialities of the scale, have also drawn attention to certain limitations. It is unsuitable for the description of organic symptoms in elderly patients (1951e) and probably fewer factors would be adequate for describing the younger psychiatric patients. The inter-correlations between the cluster scores for 100 patients were high (1953) and when submitted to factor analysis it was found that 45 per cent. of the variance was accounted for by a single general factor, which might be identified as "psychoticism", the clusters described as "acute anxiety" and "conversion

hysteria" alone having small loadings on it, a finding which suggests that analysis of the intercorrelations which would result if the factors were rotated to an oblique solution, might yield second order factors corresponding to "psychoticism" and "neuroticism". Wittenborn (1954) now intends to carry this out, which should facilitate the comparison of his findings with those of other studies (Eysenck, 1953, p. 53).

Recently Lorr *et al.* (1954) compared the second order factors derived from their analysis of the symptoms of 153 schizophrenics with those derived from their study of 423 psychotics, and also with Degan's second order factors. In spite of the differences in samples, rating methods, etc., the extent of agreement was considerable.

These factors may also be equated with certain of those found by Guertin (1952a and 1952b) in his study of schizophrenic symptoms, which is of interest because of his attempt to "type people rather than reactions" by analysing the correlations between persons ("P—analysis"). Guertin undertook this analysis (of the intercorrelations between persons) because he considered that "it is conceivable that only one of these factors (obtained from the intercorrelations of symptoms) might be seen in any individual, or many subjects might show loadings on several factors". However, the estimation of individual factor scores is a method of obtaining similar information, without introducing the complication that the tests used should be a random sample of all possible tests. The implications of "P—analysis" are controversial. For example, Guertin concluded from his analysis that the answer to the question "Is there such a thing as Schizophrenia?" is "No", although the nature of his method appears such that a general factor could not be expected to emerge.

This brief account provides evidence of the increasing concern of psychologists, utilizing factor analytical techniques, with the problems of psychiatry and, even if the stage of actually solving any of the problems has only rarely been reached, the belief in the potentialities of these techniques cannot be regarded as unrealistic.

5. PSYCHOTICISM AND NEUROTICISM

A particular problem of psychiatric classification which has not as yet been tackled by means of factor analysis is the nature of the differences between "neuroses" and "psychoses". The view that "neuroses span the bridge between . . . normal mental states and certain psychotic states" (Myerson, 1936) (which may be held without assuming the psychoanalytical concept of regression) suggests that, with increasing severity of the disorder, a neurosis should give place to a psychosis. Certainly a *diagnosis* of the one may be replaced by the other, but without adequate criteria for recognizing either it cannot be decided whether the disorder has radically changed or merely become more pronounced. Exceptions can be found to most of the criteria which have been proposed (e.g. by Nolan Lewis (1949)) and this fact has lent support to those who deny that there is any important distinction between neuroses and psychoses (e.g. Janet (1921), Diethelm (1953)), apart from a possible medicolegal one (e.g. N. Cameron, 1947).

Although the relationships between diagnostic categories and the factors found in this study will be discussed at a later date, it is relevant to mention here the possible bearing on the concepts of "Psychoticism" and "Neuroticism" of certain diagnostic groups which may be claimed as intermediate between the two. The chief example of this occurs among the Depressions. Numerous psychiatrists have maintained that there is a distinction between a "reactive"

or "neurotic" variety of depression and an "endogenous" or "psychotic" variety, e.g. Slater (1944) as well as Lange, K. Schneider, R. D. Gillespie and others. These views are discussed by A. Lewis (1934) (pp. 359-363 and 368-374) who adduces cogent arguments against there being any fundamental distinction, a conclusion in agreement with that of Adolf Meyer (see Muncie (1948) p. 285) and Mapother (1926), and among more recent writers Curran (1937), Curran and Mallinson (1941) and R. F. Tredgold (1941).

As depressions constitute a considerable proportion of functional psychiatric disorders, a failure to find support for their division into neurotic and psychotic varieties would suggest that the concepts of "neuroticism" and "psychoticism" were only of limited application. On the other hand, if evidence for these two dimensions is forthcoming it remains possible that the depressions may be divided correspondingly. Of course, in view of the failure to find any clear-cut dividing line between "psychotic" and "neurotic" depressions (e.g. Curran (1937) using Gillespie's criteria) it would be necessary to postulate a "complete gradation (from the manic-depressive psychoses) to certain minor disturbances which . . . are usually termed neuroses" (Mapother, 1926). This could imply a single continuum, but a view which accords better with recent work is merely that patients displaying the symptom of depression (in itself of little differential diagnostic value) could be ranged so as to fill every intermediate step between the most psychotic and the least neurotic on the one hand, and the least psychotic and the most neurotic on the other, their syndromes being regarded as the outcome of the blending of two or more independent components, the proportions varying widely for different patients, (but possibly varying over a smaller range in a particular person or family). This would surely help to reconcile the apparently diverse views concerning "psychotic" and "neurotic" depressions. Comparing carefully selected examples of "pure cultures" of the two varieties might well reveal significant differences between the two groups, which would be discontinuous, whereas the inclusion of selected intermediate examples could be made to yield some kind of continuous distribution. The estimation of scores for patients on the relevant factors should provide some evidence concerning the nature of this distribution. Eysenck (1955) using the method of canonical variate analysis of tests on normal, neurotic and psychotic subjects found that a high score on psychoticism was rarely accompanied by a low score on neuroticism, but it would be premature even to speculate on the relative proportions of the various components involved in the heterogeneous group of depressions. Various other relationships between particular psychoses and neuroses have been hypothesized. These have been briefly discussed elsewhere (Trouton, 1947, p. 85 ff.).

As this section is largely concerned with "psychoticism" and "neuroticism" some justification of an apparent preoccupation with these concepts is indicated. The need for a more satisfactory system of classification is generally admitted and the amount of attention devoted to this subject testifies to this. If it is sometimes useful to search for further differentiae to enable yet more subdivisions to be postulated (e.g. as by the school of Kleist) it may well be useful to proceed in the opposite direction and find if there is a fundamental division within the group of psychiatric disorders.

If there is no fundamentally reliable distinction between "Psychoticism" and "Neuroticism", continued use of the terms can only engender confusion. If, however, the varied patterns of psychiatric symptoms may be resolved into two independent components corresponding to these (even if the majority of people having a "breakdown" exhibit the presence of both, to varying extents)

there is the possibility of developing suitable objective measures which could be of value. In diagnosis these measures would serve as a method of assessing response to treatment, etc., as well as suggesting lines of research, for example (1) whether psychosomatic disorders are alternatives to neurotic or psychotic breakdowns (as is suggested by the work of Appel and Rosen (1950) and Swartz and Semrad (1951) among others), or (2) whether heredity plays a leading part in determining the variability in the relative degrees of "Psychoticism" or "Neuroticism" within an individual. The number of such projects could easily be multiplied, but a more fundamental—even if more remote—use might well be as an aid in the search for the influences underlying "Psychoticism" and "Neuroticism".

The terms "Neurotic" and "Psychotic", however, are still widely used and often without disagreement about their applicability to a particular patient. This may have some fundamental significance and could be investigated either by a consideration of the differences between patients who belong undisputably to one or other of the two categories, or by classifying the salient facts about both (as in this factor analytical study) and ascertaining if this empirically established principle of classification corresponds with the traditional psychiatric one. These two approaches may be combined, as in Criterion Analysis (Eysenck, 1950). The experimental evidence so far certainly has been against the hypothesis that neuroticism and psychoticism are on the same continuum (for example some tests differentiate between normal subjects and neurotics but not between normals and psychotics). Canonical variate analysis of test scores (Lubin, 1951, Eysenck, 1955) has also given results contrary to the "single continuum" hypothesis. It was not expected, therefore, that a general factor would emerge in factorial studies of tests or ratings of patients including both those diagnosed as psychotic and those diagnosed as neurotic.

6. PROCEDURE

(i) *Description of Item Sheet*

This is an eleven page form which is filled in for every in-patient by the doctor responsible. It consists of two parts:

I. History and Previous Personality, and

II. Findings in Hospital: Treatment: Outcome.

There are over 500 items, intended to cover every psychiatrically significant aspect of the patient's history, symptoms and course of illness. Each item is scored for its presence or absence and the form checked for completeness by a clerical worker and for inaccuracies by the consultant in charge of the patient. Any identifying date (apart from the hospital number) is excluded. The information is then transferred to punched cards (formerly Powers-Samas, now Hollerith).

(ii) *Selection of the Variables*

The inclusion of 500 items would require the computing of many thousands of correlations, and so a maximum of 45 items was decided upon.

The guiding principle in the selection of appropriate items being to represent the main functional psychiatric disorders, descriptions of these in the psychiatric and psychological literature were compared (the lists provided by Cattell (1946) being especially useful); the possible range was narrowed by attempting to include only items of the same level of generality and especially items similar to those which, in previous factor analytical studies, have been of use in defining factors such as neuroticism.

Several other considerations influenced the selection. One of these was the avoidance of "contamination" as far as possible (e.g. it is likely that a patient diagnosed as Manic would have the symptom "Manic or hypomanic" recorded as present whereas similar behaviour in a patient diagnosed as Schizophrenic might well not appear in this category but instead be recorded as "Non-manic euphoria", "Excitement", "Overactive", etc. Such items were combined, a procedure which was also necessitated where it was thought that two terms were so closely related that there would not be reliable discrimination between them. It may seem that a loss of important detail results from this, e.g. the combination of the four items:

- (a) Over-active
 - (b) Excitement
- (from the section on disorders of behaviour)

and

- (c) Manic or hypomanic
- (d) Non-manic euphoria

to make a single composite item (No. 23), might be considered to blur the distinction between the mania characteristic of the manic-depressive psychosis and the excitements which may occur in schizophrenia. The two are not, however, always distinct, and Bonner and Kent (1936) found much similarity and overlap between the two supposed types, in spite of their very careful exclusion of patients whose diagnoses were not reasonably certain. In certain instances closely related phenomena were included together if they were considered to be important diagnostically but otherwise of too low incidence for inclusion: in order that these composite items should be psychiatrically meaningful, the requirement was laid down for symptoms that they should have been shown in previous studies to occur together commonly (e.g. the item "Posturing, grimacing, mannerisms, stereotypy"—incidentally already composite—was combined with "Catatonic disturbance of muscle tone"); for items from the past history to be meaningfully combined the requirements were simpler, more specific details being subsumed under a single heading (e.g. the composite item No. 10 in this study, where it is described as "Unsatisfactory home adjustment as an adult", is made up of the three items: "Marital sexual intercourse unsatisfactory", "Unsatisfactory or disturbed emotional relationship with marital partner", and "Children rejected or in other unsatisfactory emotional relationship", and is scored as present if any of its three component items is recorded as present). No symptom or item was included in more than one composite item.

(iii) *Selection of Sample*

Owing to the arbitrary nature of any adjustment to the relative proportions of the diagnostic groups included in the sample, no selection was exercised. The study was, however, confined to 819 males, aged 16–59 inclusive, all having a diagnostic code number corresponding to any organic disorder being excluded. Although there is a tendency to neglect the study of mental symptoms when the condition has been shown to be organic in origin (Golla, 1938), the inclusion of patients with organic disorders might render the findings extremely complicated. Likewise the study was confined to males, Wittenborn (1953), for example having found evidence that the patterns of symptoms in the two sexes showed some marked differences.

(iv) *Frequencies of the Items*

A preliminary study of 100 Item Sheets had indicated that a larger scale study was feasible, but had also made clear the difficulty of selection of appro-

priate symptoms, owing to the low incidence of some of them. The cards were therefore sorted to ascertain these incidences (see Table I). The sample consisted of only 700 of the 819 cases included in the main study as at this stage it had not been decided that Personality Disorders were to be included.

(v) *Computation*

In spite of the *a priori* criticism of the use of tetrachoric correlations in work of this nature, the alternatives which have been advocated such as the use of phi coefficients (e.g. Sandler, 1954) or of percentages (Burt, 1954) are not devoid of disadvantages and, without a ready means of calculating the correlations such as is provided by Thurstone's Diagrams, a study of this scale could not have been carried out. Care was taken that none of the item frequencies fell below 10 per cent. This necessitated combining certain items as described above; however, most of the frequencies were well above the 10 per cent. level. Each correlation used was the average of two estimates from Thurstone's Diagrams.

The correlation matrix is given in Table VI. It was analysed by Thurstone's (1947) centroid method of multiple factor analysis. Six centroids were extracted accounting for 45.3 per cent. of the variance. The residuals after the extraction of six centroids were of almost negligible magnitude. No attempt to test these residuals for significance was made since it was felt that any effort to identify even as many as six factors from a matrix of tetrachoric correlations, however large the sample, would be of doubtful validity from a psychological point of view. Moreover, had it been the aim of the investigators to extract the maximum number of significant factors, a more accurate technique than Thurstone's, and one requiring much more time and computation would need to have been employed.

The matrix of centroid loadings is given in Table III. An orthogonal transformation of these loadings was sought which would yield factors conforming as far as possible to present psychological knowledge and psychiatric practice and at the same time aim at economy of description. The transformation matrix employed is given in Table IV and the resulting rotated factor matrix in Table V. It is intended subsequently to examine the validity of the rotation employed here when further relevant clinical and psychological information is examined.

7. DESCRIPTION AND INTERPRETATION OF THE ROTATED FACTORS

(i) FACTORS I AND II: PSYCHOTICISM AND NEUROTICISM

Factor I has high loadings on symptoms such as "Socially withdrawn" (item 26), "Ideas of reference" (38), "Hallucinations" (40), "Delusions of guilt" (39) and "Psychotic" (2). This factor may confidently be labelled "Psychoticism".

Factor II has positive loadings chiefly on the various neurotic items, e.g. "childhood neurotic traits" (11), "lifelong hysterical symptoms" (12), "lacks confidence" (9), etc. Its close similarity to the well-established factor of neuroticism makes its identification apparent.

The relationship between the loadings on I and II is shown in Diagram 1. There is little overlap between the factors the only items having positive loadings on both being (9) "lacks confidence", (27) "obsessions and compulsions", (29) "depressed" and (33) "irritable" (cf. Slater's (1943) view that obsessional "neurosis" should be classed as a "psychosis"). It is unlikely that the distinctions of factors I and II can be explained either by the fact that some of the neurotic symptoms had to be taken from Part I of the Item Sheet which deals with the

FACTORS I AND II

II

Neuroticism

Anxiety symptoms, lifelong or episodic.

14

Hysterical symptoms, lifelong or episodic.

12

Unsatisfactory early life.

6

Symptoms of over 12 months' duration

before admission.

17

Family History of abnormal personality (e.g. Psychopathy,

Functional disturbances in systems other than the nervous.

5

21

Family History of neurosis.

4

8

Work position falling and/or frequent unemployment

due to instability of patient.

10

Unsatisfactory home life as an adult.

Neurotic traits in childhood.

11

Definite mood variations before present illness.

15

Unsatisfactory adolescent adjustment.

7

27

Obsessional symptoms.

13

Lacks confidence when in society.

16

Energy output low.

9

Irritable.

33

Depressed.

29

Severe insomnia at any time during illness.

41

Agitated.

24

Constitutional causes important or dominant.

19

Suicidal feelings.

34

Delusions of guilt, self-reproach, unworthiness.

37

Impulsive and/or aggressive

25

Psychoticism

I

Family History of Psychosis.

3

Gross disturbance of weight and/or food intake.

42

31

36

36

36

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26 Socially withdrawn.

32 Suspicious.

Psychogenic impairment of thought or memory.

Mood disturbances.

Retarded activity.

22 Motor disturbances (e.g. posturing, grimacing and catatonic disturbances).

39 Delusions.

40 Hallucinations.

38 Ideas of reference.

20

Precipitating psychological and social causes unimportant.

45

Recovered or much improved at time of discharge.

44

Denial, indifference or unawareness of symptoms.

44

Overactive, excited, manic or hypomanic, non-manic euphoria.

23

Gross disturbance of weight and/or food intake.

42

Family History of Psychosis.

3

31

36

36

36

36

36

Schizophrenic type of thought disorder.

35

Psychotic vs. Non-psychotic.

2

Previous History, or by the fact that some of the symptoms with loadings on factor I represent the extremes of that particular aspect of the disorder, (cf. the discovery of factors attributable largely to difficulty levels (Peak, 1953, p. 276)). The factor loadings in items 3 and 4 give incidental support to the correctness of the interpretation.

	I	II
(3) Family History of Psychosis	.28	— .02
(4) Family History of Neurosis	— .03	.32

Factors I and II are entirely congruent with the view that psychoticism and neuroticism are independent dimensions.

(ii) DESCRIPTION OF THE OTHER FACTORS

Factor III has positive loadings on symptoms such as "Schizophrenic type of thought disorder", "Posturing and catatonic disturbances of muscle", "Hallucinations", etc., and also on items such as "Work record declining", "Symptoms for over a year before admission", and "Unsatisfactory adolescent adjustment". The positive loadings are thus descriptive of some of the features of schizophrenia.

On factor III there are also some high negative loadings for symptoms such as "Delusions of guilt", "Depressed", "Anxious", and also for the item "Recovered or much improved in hospital". Thus the negatively loaded items are descriptive of some of the features of a "psychotic depression".

Factor IV which will be referred to as "inactivity—withdrawal" includes symptoms such as "Socially withdrawn", "Retarded activity" at the positive end and at the opposite extreme symptoms such as "Impulsive and aggressive" and "Mood rapidly changing or inappropriate". Although not as well established as the preceding factors the continuum is not only semantically satisfactory but necessary to supplement the other factors if some of the different varieties of Depression and Schizophrenia are to be described. For example, the factors III and IV together divide the items with high loadings on I (psychoticism) so that it is possible to describe several different psychotic syndromes according to the loadings on III and IV, e.g. Agitated Depression would be similar to Depression with Retardation in that there would be positive loadings on I, zero on II, negative on III but on IV the loadings would tend to be negative for the former (with agitation) and positive for the latter (with retardation). This may be considered to be consistent with D. E. Cameron's (1945) theory that the relationships between excitement, anxiety and depression "may be expressed in terms of the varying dominance of the two components of tension, namely inhibition and facilitation" (not in Pavlov's sense).

The remaining factors contribute little to the variance and are probably unimportant. V may represent Hypochondriasis, and VI Obsessionality (the latter is also descriptive of some of the features associated with involutional melancholia). There are, however, too few items with loadings on these factors for either of them to be identified with conviction.

The principal finding of this study, indicating that neuroticism and psychoticism are independent dimensions was discussed when factors I and II were described. It remains to consider briefly the possible relationship of the factors to the findings in certain other researches in psychology and psychiatry, and also their relevance to the problems of psychiatric classification.

(iii) PSYCHIATRIC SIGNIFICANCE OF FACTORS III AND IV

(a) *Manic-Depressive Psychosis*

As manics occur less often than depressives and schizophrenics, and their

symptoms have only a meagre representation in the Item Sheet, the failure to obtain a bipolar manic-depressive factor is not unexpected. Wittenborn (1953), however, found manic and depressive features at the opposite poles of the same factor, and regarded this as supporting the Kraepelinian conception of a functionally unitary disease. Kraepelin's arguments for these being "manifestations of a single morbid process" were that there were (1) "common fundamental features"; (2) transitions between the conditions; (3) a uniform prognosis and (4) hereditary influences (E. Kraepelin, 1921). Wittenborn's inference would have more weight if it could be assessed to what extent this bipolarity is the result of the method of analysis employed, and of the trivial fact that synonyms will, in any case, tend to emerge from such analyses with signs opposite to their antonyms. However, the significance of this bipolarity probably cannot be explained away entirely in terms of statistics and semantics, in view of Degan's finding that depression was not a negative component of the factor of "Hyper-excitability", which he claimed was a "challenge to the common classification of mania and depression as affective disorders of opposite polarity" (Degan, 1952). The custom of labelling depressed patients "manic-depressive" even though the chances are that they will never display mania has also been questioned by some psychiatrists (e.g. Bond and Partridge, 1924; N. Cameron, 1942) who find little support for the functional unity of these two conditions, although the psychoanalytical theory of a manic defence against depression does provide a hypothetical link (Klein, 1940). Moore (1941) found differences in prepsychotic personality between manic-depressive patients. If the genetic evidence were in favour of a single dominant gene being responsible for the two conditions, this, indeed, would be in favour of the Kraepelinian conception, but Penrose (1944) considers that "it might be wisest to presume that the mode of inheritance is multi-factorial".

The implication of the foregoing is that mania and depression cannot be represented by a common dimension (apart from psychoticism) and it seems reasonable to regard their respective dimensions, provisionally, as orthogonal; this provides a framework within which the occurrence of mixed cases can be most readily described.

(b) *Depression and Schizophrenia*

The bipolar arrangement on factor III of certain schizophrenic and depressive symptoms might suggest that depression and schizophrenia cannot co-exist. This is not necessarily implied, even if such a finding were confirmed in different studies. In the first place, only a partial description of the disorders can be provided in terms of one factor; secondly it is possible that the display or recognition of symptoms at one end of this factor may be marked by the symptoms at the other end (E.C.T. may, for example, lead to the display of more florid schizophrenic behaviour as the depressive element becomes diminished). However, this bipolar arrangement might conceivably be taken as suggesting some more fundamental relationship between depression and schizophrenia. T. V. Moore mentioned this possibility but without proposing what the nature of this relationship was. He wrote "the evident meaning of the supergeneral factor . . . is that these two psychoses are not more or less unrelated conditions, such as *paresis* or *chronic alcoholism*, but that *manic-depressive* and *praecox* conditions have something in common, so that, from this point of view, they are generically identical though specifically different" (Moore, 1933). The findings of B. Schultz (discussed by Slater, 1950) which suggest that "there are genetical factors common to both schizophrenic and affective disorders" would, if confirmed, provide a basis for Moore's findings.

8. TYPE OF PSYCHIATRIC CLASSIFICATION IN RELATION TO FACTOR ANALYSIS

Although the empirical comparisons of the factorial, clinical and behavioural classifications will be described at a later date, some discussion is necessary of the different types of classification in use clinically and those which may be derived by means of factor analysis.

First, psychiatric diagnosis consists basically of assigning a patient to a single category, although mixed diagnoses are recognized (particularly by those influenced by the views of Adolf Meyer), yet with some reluctance probably based on the widespread opposition to multiple diagnoses in general medicine. According to the factor analytical scheme, on the other hand, every patient is assumed to have some position on each of the dimensions. Secondly, in contrast to the clinical method, the latter estimate is *quantitative* rather than *qualitative*.

The two methods resemble each other in both being largely based on symptoms, although past history, aetiology, etc., are also included. In this respect there is an analogy to the Linnaean system, in which morphology chiefly but also the life history are considered, but the analogy breaks down because in biological classification the categories should be separated from the neighbouring ones by "reasonably sharp discontinuities of character" (Calman, 1949). Even in biology, however, in spite of evolution having proceeded largely in a continuously diverging manner, the traditional logical method of classification is not strictly practicable (Stebbing, 1942, p. 439). Nevertheless the hierarchical arrangement (Phylum, Class, Order, Family, Genus, Species, etc.) is a striking feature of it, which has only a rudimentary equivalent in the classifications derived from clinical or factor analytical studies. Pophal (1925) compared the then current methods of classifying patients to classifying "humans into Europeans, Blacks, Vegetarians and Homosexuals". This parodies the overlapping nature of diagnostic groups, but does indicate the necessity for reducing this by aiming to establish a single *fundamentum divisionis*, which is essential at each level of an ordered classification unless the relationships between the classes are to be obscured. In psychiatry a mixed diagnosis such as "Depression in a Hysterical Psychopath with Schizophrenic Features" gives little indication of the relative importance of the components. Nor does a Thurstonian multiple factor analysis resulting in first order orthogonal factors provide a much clearer framework, but the still controversial method of deriving second order factors by analysing the intercorrelations of oblique first order factors does provide a hierarchical arrangement, even though it may appear that too much is built on insecure foundations.

SUMMARY

A report is given of a study on psychiatric classification which consisted of a factor analysis of the inter-correlations between 45 variables derived from the Item Sheet used at the Bethlem Royal and Maudsley Hospitals. The sample consisted of 819 male in-patients aged 16-59, having non-organic psychiatric disorders. The variables included the main symptoms and items from the past history of psychotic and of neurotic patients.

Using Thurstone's centroid method of multiple factor analysis 6 factors were extracted accounting for 45 per cent. of the variance. The first two of the orthogonally rotated factors were identified as "Psychoticism" and "Neuroticism" and were in accordance with the hypothesis that these are independent dimensions.

In a subsequent research the classification of patients suggested by this study will be compared with the classifications derived independently from both clinical and psychological investigations.

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TABLE IA

*Main Diagnoses of the Sample of 700 Males (Aged 16-59) to which
Tables IB and IC Refer*

Psychotic									
Schizophrenia	..	..	..	..	..	..	..	..	185
Manic and circular psychoses	..	..	..	..	..	..	..	..	33
Depressive psychoses (including Involutional Melancholia)	..	..	..	..	..	..	..	..	123
Paranoia	..	..	..	..	..	..	..	..	12
Neurotics									
Anxiety states (including phobic)	..	..	..	..	..	..	..	..	114
Obsessional and other psychoneuroses	..	..	..	..	..	..	..	..	80
Hysteria	..	..	..	..	..	..	..	..	35
Neurotic depressions	..	..	..	..	..	..	..	..	116
Diagnosis Uncertain	..	..	..	..	..	..	..	..	2

TABLE IB

*Classified List of Variables included in the Study, with their Incidences
in 700 Males (as in Table IA)*

Item		Psychotic Symptoms							Incidence
Depression									
22	Retarded activity	..	..	..	..	..	..	..	180
24	Agitated	..	..	..	..	..	..	..	149
29	Depressed	..	..	..	..	..	..	..	434
34	Suicidal	..	..	..	..	..	..	..	119
37	Delusions of guilt	..	..	..	..	..	..	..	127
Mania and Excitement									
*15	Previous history of mood variations	..	..	..	..	..	..	..	333
23	Over-active, excited, manic, etc.	..	..	..	..	approx.	..	..	100-150
33	Irritable	..	..	..	..	..	..	..	167
41	Insomnia	..	..	..	..	..	..	..	329
Schizophrenia									
39	Other delusions	..	..	..	..	..	approx.	..	150
40	Hallucinations	..	..	..	..	..	..	..	114
35	Schizophrenic thought disorder	..	..	..	..	..	..	..	103
31	Mood disturbance	..	..	..	..	..	..	..	157
28	Posturing, grimacing, etc.	..	..	..	..	..	..	..	83
Other Symptoms (chiefly occurring in psychosis)									
38	Ideas of reference	..	..	..	..	..	..	..	133
25	Impulsive and aggressive	..	..	..	..	..	..	..	148
44	Denial of symptoms	..	..	..	..	..	..	..	91
26	Social withdrawal	..	..	..	..	..	..	..	255
43	Hypochondriacal attitude	..	..	..	..	..	..	..	220
32	Suspicious	..	..	..	..	..	..	..	199
36	Psychogenic thought and memory impairment	..	..	..	..	..	approx.	..	120
21	Functional disturbances in systems other than nervous	..	..	..	..	..	..	..	119
42	Gross disturbance of weight or food intake	..	..	..	..	..	..	..	75
Neurotic Symptoms									
*11	Childhood neurotic traits	..	..	..	..	..	approx.	..	120
Hysteria									
*12	Previous hysterical symptoms	..	..	..	..	..	..	..	273
*16	Low energy and lacks effort	..	..	..	..	..	..	..	102

TABLE 1B (continued)

Dysthymia

*14	Previous anxiety symptoms	..	..	..	..	..	101
*19	Lacks confidence	..	..	..	..	..	336
27	Compulsions and obsessions	..	..	..	..	..	—
*13	Previous obsessional symptoms	..	..	..	..	..	167
30	Anxious	..	..	..	..	..	390

Other Variables (all from past history)

1	Age 16-39	..	..	..	..	..	—
2	Psychotic vs. non-psychotic (including Personality Disorders)						—

Family History

3	Family history of psychosis	..	..	..	..	..	108
4	Family history of neurosis	..	..	..	..	..	128
5	Family history of personality deviation or psychopathy	approx.					150

Previous Adjustment

6	Unsatisfactory early family relationship	..			approx.	200
7	Unsatisfactory adjustment in adolescence	..			approx.	200
8	Unsatisfactory work record	..	..		approx.	269
10	Unsatisfactory marital and home relationship				approx.	200

Onset of Illness

17	Symptoms for over 12 months	..	..	..	..	..	319
**18	Sudden onset of present illness	..	..	..	..	..	119

Causes of Illness

19	Constitutional causes important or dominant	..	..	..		468
20	Precipitating psychological causes unimportant	..	..			112

Outcome

45	(Recovered or much improved)	..	..	..	..	..	—
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* Symptoms having an asterisk by them are from the Past History.

** The sign of this variable was changed subsequently (see Table V).

TABLE 1C

Symptoms Excluded Because of Low Incidence (N=700)

	Incidence
Aggressive and assertive in society	82
Psychosomatic disorders	72
Previous suicidal attempts (demonstrative)	22
History of frequent accidents	13
Stupor	23
Self injury	21
Fugues and automatisms	14
Negativism	17
Disorientation	19
Manifest superficial motives	58
Depersonalization	40
Non-serious suicidal attempts	approx. 40
Incontinence	14
(Severe emotional shock in childhood	1)

TABLE II

Item Sheet Analysis: Variables Included in the Factor Analysis

Number of Items in Factor Analysis		
1		Age (16-39) vs. (40-59)
2		Psychotic vs. non-psychotic (i.e. neurosis and personality disorders)
3	Family History	Family history of psychosis
4	of Psychiatric	Family history of neurosis
5	Disorder	Family history of abnormal personality (e.g. psychopathy, alcoholism)
6		Unsatisfactory early life
7		Unsatisfactory adolescent adjustment
8	Previous	Work position falling and/or frequent unemployment due to instability of patient
9	Adjustment	Lacks confidence when in society
10		Unsatisfactory home life as an adult
11		Neurotic traits in childhood
12		Hysterical symptoms, lifelong or episodic
13		Obsessional symptoms, lifelong or episodic
14	Previous	Anxiety symptoms, lifelong or episodic
15	Symptoms	Definite mood variations before present illness
16		Energy output low, lacks effort for success and achievement
17		Symptoms of over 12 months' duration before admission
18	Causes and	Gradual onset of illness
19	Onset of	Constitutional causes important or dominant
20	Illness	Precipitating psychological and social (environmental) causes unimportant
21		Functional disturbances in systems other than the nervous
22		Retarded activity
23		Overactive, excited, manic or hypomanic, non-manic euphoria
24		Agitated
25		Impulsive and/or aggressive
26	Symptoms	Socially withdrawn
27	of Present	Compulsive acts and/or obsessional thoughts
28	Illness	Motor disturbances (e.g. posturing, grimacing and catatonic disturbances)
29		Depressed
30		Anxious
31		Mood disturbances (inappropriate or rapidly changing)
32		Suspicious
33		Irritable
34		Suicidal feelings, intentions or serious attempts
35		Schizophrenic type of thought disorder
36		Psychogenic impairment of thought or memory
37		Delusions of guilt, self-reproach, unworthiness
38		Ideas of reference
39		Delusions (other than those included in 37 and 38)
40		Hallucinations
41		Severe insomnia at any time during illness
42		Gross disturbance of weight and/or food intake
43		Hypochondriacal attitude towards illness
44		Denial, indifference or unawareness of symptoms
45	Outcome in Hospital	Recovered or much improved at time of discharge

TABLE III

Unrotated Factor Matrix

Variables	I	II	III	Factors IV	V	VI	h ²
1	-.063	-.175	-.497	-.269	.302	.059	.449
2	.822	-.095	.097	-.094	.078	-.318	.810
3	.248	.122	-.155	-.105	.056	.252	.178
4	-.186	.264	-.042	.276	-.157	.022	.208
5	-.202	.286	.168	-.155	.068	.196	.218
6	-.239	.403	.124	-.070	-.046	.188	.277
7	-.076	.397	.335	.187	-.260	.078	.384
8	-.170	.257	.394	.091	.128	.127	.291
9	.038	.341	.041	.364	-.319	.190	.390
10	-.322	.099	-.150	-.306	.263	.105	.310
11	-.229	.425	.182	.033	.237	.099	.333
12	-.458	.358	.188	-.053	.159	-.131	.418
13	.082	.383	.283	-.054	.081	.298	.332
14	-.453	.568	-.127	-.181	+.140	.019	.596
15	-.144	.418	.081	-.441	-.100	.231	.460
16	-.132	.266	.239	.324	.082	.150	.279
17	-.405	.257	.291	.037	.098	.291	.411
18	.036	.202	.091	-.185	-.122	.335	.211
19	.231	.241	-.042	.041	.210	.324	.264
20	.270	-.156	-.170	.091	.198	.119	.188
21	-.278	.221	-.249	.235	.215	-.332	.400
22	.581	.182	-.307	.266	-.107	.213	.592
23	.407	.089	.220	-.371	.328	-.272	.541
24	.199	.323	-.259	-.320	.155	-.238	.394
25	.469	.299	.406	.359	.152	-.118	.640
26	.534	.306	-.047	.491	-.271	.106	.707
27	.084	.485	.357	.096	.138	.298	.487
28	.604	.178	.396	.195	.263	.026	.662
29	.158	.330	-.643	-.051	-.336	.087	.671
30	-.227	.360	-.406	.116	-.215	-.265	.476
31	.458	.255	.502	-.113	.173	-.131	.586
32	.510	.290	.234	-.149	-.068	-.214	.472
33	.146	.343	.240	-.333	-.119	-.167	.350
34	.290	.290	-.301	-.270	-.091	.107	.351
35	.773	-.088	.475	.240	.026	.067	.893
36	.487	.235	.046	.175	.151	.081	.354
37	.440	.374	-.477	.056	-.235	.028	.620
38	.634	.048	.258	.221	-.241	-.200	.618
39	.688	.142	.149	.159	.076	-.231	.600
40	.644	.092	.333	.164	.066	-.278	.642
41	.171	.320	-.472	-.269	.232	-.115	.494
42	.342	.186	-.336	.141	.235	.137	.359
43	-.233	.324	.295	.190	.250	-.372	.483
44	.294	-.096	.597	-.142	.201	.263	.582
45	.054	-.157	-.542	.133	-.253	-.039	.404

TABLE IV

Orthogonal Rotation Matrix

.866	-.500	0	0	0	0
.500	.860	0	0	0	0
0	0	.793	-.346	-.243	.439
0	0	.370	.742	.520	.205
0	0	.349	-.399	.569	.629
0	0	.337	.413	-.589	.608

TABLE V
Orthogonal Rotated Factor Loadings

Variables			I	II	III	IV	V	VI	h ²
1	..	..	·142	·120	·368	·123	·118	·499	·448
2	..	..	·664	·493	·176	·003	·215	·219	·809
3	..	..	·276	·018	·058	·056	·134	·278	·178
4	..	..	·029	·322	·022	·291	·051	·124	·208
5	..	..	·032	·349	·166	·119	·198	·120	·218
6	..	..	·005	·468	·120	·001	·203	·045	·276
7	..	..	·133	·382	·271	·159	·178	·302	·385
8	..	..	·019	·308	·433	·068	·050	·034	·291
9	..	..	·203	·276	·120	·461	·114	·174	·388
10	..	..	·229	·247	·105	·237	·035	·358	·310
11	..	..	·014	·483	·107	·097	·220	·176	·334
12	..	..	·218	·539	·141	·222	·095	·061	·420
13	..	..	·120	·373	·116	·149	·089	·367	·332
14	..	..	·108	·718	·210	·026	·154	·017	·596
15	..	..	·084	·434	·056	·220	·442	·133	·460
16	..	..	·019	·296	·389	·187	·068	·029	·280
17	..	..	·222	·425	·377	·007	·167	·104	·410
18	..	..	·132	·157	·074	·018	·385	·125	·212
19	..	..	·321	·093	·164	·095	·040	·339	·264
20	..	..	·156	·270	·008	·096	·131	·253	·188
21	..	..	·130	·330	·147	·037	·500	·005	·399
22	..	..	·594	·133	·111	·435	·026	·143	·593
23	..	..	·397	·126	·060	·595	·101	·021	·542
24	..	..	·334	·180	·350	·308	·125	·132	·394
25	..	..	·556	·024	·202	·516	·130	·081	·640
26	..	..	·615	·002	·086	·533	·050	·186	·707
27	..	..	·315	·378	·099	·263	·040	·405	·487
28	..	..	·612	·148	·486	·087	·139	·033	·661
29	..	..	·302	·207	·616	·355	·113	·135	·671
30	..	..	·061	·425	·529	·031	·072	·094	·476
31	..	..	·524	·008	·372	·381	·006	·169	·587
32	..	..	·587	·004	·034	·253	·047	·246	·472
33	..	..	·298	·224	·031	·351	·201	·214	·349
34	..	..	·396	·106	·334	·015	·182	·196	·351
35	..	..	·625	·463	·497	·031	·014	·201	·894
36	..	..	·539	·040	·127	·020	·213	·011	·354
37	..	..	·568	·104	·490	·206	·030	·057	·620
38	..	..	·573	·275	·135	·088	·033	·432	·618
39	..	..	·667	·221	·125	·059	·226	·191	·600
40	..	..	·604	·242	·254	·135	·206	·308	·643
41	..	..	·308	·192	·431	·176	·176	·339	·494
42	..	..	·389	·010	·086	·184	·208	·350	·358
43	..	..	·040	·397	·202	·010	·532	·021	·484
44	..	..	·207	·230	·579	·284	·259	·053	·582
45	..	..	·032	·163	·580	·174	·059	·082	·404

TABLE VI
Correlation Matrix

Variables	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	..														
2	..	149													
3	..		028												
4	..		335												
5	..			046											
6	..				015										
7	..				031										
8	..				079										
9	..				066										
10	..					222									
11	..					193									
12	..					124									
13	..					036									
14	..					138									
15	..					162									
16	..					409									
17	..					154									
18	..					235									
19	..						048								
20	..						173								
21	..						439								
22	..						086								
23	..							137							
24	..							072							
25	..							269							
26	..							032							
27	..								217						
28	..									262					
29	..										085				
30	..											254			
31	..												254		
32	..													331	
33	..														309
34	..														205
35	..														523
36	..														
37	..														
38	..														
39	..														
40	..														
41	..														
42	..														
43	..														
44	..														
45	..														

Variables	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
1	..														
2	..	-150	018	-010	003	170	154	052	-099	243	-248	-197	-013	-379	285
3	..	110	217	214	-271	-318	295	-417	-399	-140	-246	-315	011	-571	-047
4	..	025	-101	-004	280	123	-141	159	050	163	137	087	130	135	155
5	..	069	161	-013	062	-060	118	009	-176	059	-239	060	176	-047	091
6	..	175	211	-090	193	-062	064	-098	-010	-073	106	-129	095	-017	-011
7	..	029	308	-109	158	-148	038	-156	-024	-068	027	003	150	-012	039
8	..	340	154	-077	045	-142	-047	-033	-033	-067	126	173	081	099	-102
9	..	403	413	-055	062	-103	-053	-023	-081	-049	193	020	-093	137	-119
10	..	269	022	-074	148	-103	020	143	-229	-042	-050	432	108	092	160
11	..	024	204	-194	-004	032	216	-167	-075	139	-070	-305	033	-345	084
12	..	117	184	-126	047	-123	039	-198	-007	002	031	069	233	-025	002
13	..	114	222	-096	-024	-146	211	-144	-035	006	003	-308	049	-122	-172
14	..	-111	124	-152	210	007	007	150	052	096	-003	019	729	042	118
15	..	103	236	-100	-054	-229	185	-127	-166	198	-088	-080	204	-242	199
16	..	125	106	-260	139	-189	-104	-026	188	144	153	-111	060	-093	191
17	..		156	-069	213	-036	095	048	-098	-090	025	166	-001	110	-110
18	..			-300	-093	-163	022	028	-310	-187	-115	-041	-062	142	-144
19	..				-063	062	180	-124	054	012	-017	-105	-197	-012	-100
20	..					195	-035	186	088	004	173	121	181	295	170
21	..						-087	237	113	-004	033	122	099	050	009
22	..							-141	-075	094	-295	-003	-010	-107	114
23	..								-122	009	050	667	271	284	505
24	..									354	588	-076	029	465	-224
25	..										236	037	206	015	260
26	..											113	001	481	-177
27	..												296	402	252
28	..													103	297
29	..														-266
30	..														385

Variables	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45
1	..														
2	..	-416	-031	-090	004	-425	-017	116	-299	-117	-256	307	205	168	-127
3	..	-336	-406	-082	-193	-795	-274	-360	-567	-661	-499	0	-217	245	-433
4	..	130	007	-053	209	-004	023	237	079	098	065	135	142	-009	068
5	..	-121	-032	-006	-048	-069	043	045	-051	007	-095	-046	-098	203	-157
6	..	022	070	165	-025	-111	-032	-100	-060	-153	-095	122	-084	-011	004
7	..	-024	0	097	058	-180	-030	-072	-189	-121	-101	0	031	009	-068
8	..	178	035	185	001	010	098	032	032	-036	057	-093	032	-037	104
9	..	110	068	184	-154	036	034	-175	-010	-087	006	-096	-100	-053	246
10	..	067	010	-006	082	186	079	081	212	068	081	-131	101	119	-024
11	..	-175	-026	053	-053	-307	-075	-084	-327	-285	-341	178	001	168	-051
12	..	089	-034	138	019	-081	-059	-006	-047	-141	-097	-055	-170	-005	-103
13	..	166	-151	083	-035	-343	-046	-293	-381	-210	-061	001	-100	245	-094
14	..	-010	-007	-034	204	-220	-082	173	-230	-088	-269	146	015	107	-138
15	..	-118	-098	061	144	-399	-083	085	-285	-252	-288	154	-085	268	-300
16	..	136	059	200	175	-143	-084	117	-143	-149	-199	169	-082	0	072
17	..	064	001	-024	-155	003	130	-071	005	-032	-062	-169	-013	114	103
18	..	-049	-149	105	-075	-194	-189	-201	-137	-209	-105	-190	-047	001	120
19	..	-066	-127	-177	-076	-076	134	-180	002	-047	-081	-027	020	139	-147
20	..	093	098	-042	140	147	024	200	063	224	162	179	219	-001	037
21	..	-011	049	-099	013	225	099	027	194	115	041	114	117	-010	-057
22	..	-222	-086	-066	-073	-303	-017	133	-111	073	-120	106	235	440	-296
23	..	094	246	-022	218	390	475	501	334	340	305	130	426	-011	-016
24	..	460	258	245	028	251	227	073	205	310	312	265	058	-063	256
25	..	095	201	264	226	004	215	307	005	135	115	366	186	139	-056
26	..	567	499	506	243	347	299	039	291	304	287	146	094	-188	366
27	..	116	304	137	051	491	413	365	474	447	300	087	300	-032	028
28	..	074	024	-049	268	-129	097	248	-089	020	-064	202	253	097	-173
29	..	569	297	077	-005	675	447	048	441	492	556	-103	234	-129	452
30	..	-265	093	058	465	-261	123	600	049	030	-129	433	286	114	-429
31	..	-254	-011	074	107	-398	-084	289	-133	-130	-208	286	-090	292	-353
32	..		311	223	221	634	376	020	344	373	497	001	-094	-019	362
33	..			475	016	414	267	264	604	607	483	076	078	-028	305
34	..				103	068	139	054	074	124	049	109	031	043	147
35	..					-015	119	486	-007	039	029	381	275	-083	-138
36	..						553	-008	576	682	656	-127	086	-315	488
37	..							249	327	321	452	151	299	046	222
38	..								247	323	202	348	300	058	-197
39	..									636	565	-125	-038	-164	107
40	..										673	090	122	030	263
41	..														

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HYPNAGOGIC IMAGERY AND MESCALINE*

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INTRODUCTION

SIMILARITY between certain of the visual effects of mescaline and hypnagogic imagery has been independently noted by several investigators, one of the earliest of these being Weir Mitchell (1896). Our own research group first became interested in hypnagogic experiences when one of the writers, as subject, in seeking to communicate the character of his mescaline visions, likened them to images he had encountered just before sleep. This led to an investigation of hypnagogic imagery as such, the results of which have been published elsewhere (McKellar and Simpson, 1954). Further experiments with mescaline, and consideration of the relevant literature of the two fields, suggest that the mescaline-induced and hypnagogic states are more than superficially alike, and that a comparison may illuminate the processes at work in each.

In the present paper such a comparison will be attempted. No theoretical inferences will be drawn, however, these being more relevant to a general theory of mescaline intoxication elsewhere presented (Ardis and Drewery, 1954).† Our paper will deal principally with a comparison of hypnagogic visual phenomena and those induced by mescaline. Many of these comparisons may apply equally to other mental phenomena, and for that matter to other hallucinogens: Mayer-Gross *et al.* (1954) emphasize that the sensory phenomena produced by lysergic acid diethylamide and those of mescaline are "almost identical".

Hypnagogic imagery is not necessarily visual, but may be auditory, kinaesthetic or of some other sense mode. It occurs in the drowsy state prior to deep sleep. The experiences are distinguishable from the imagery of dreams, from the images of waking thought, and from normal sense perception. Less obvious is their differentiation from eidetic imagery, and from hallucination in certain psychotic and other clinical conditions. Galton (1883, p. 118) speaks of "the continuity between all the forms of visualization, beginning with an almost total absence of it, and ending with a complete hallucination". Our observations are in close accord with this standpoint and, in the case of hypnagogic imagery, we would suggest that these phenomena have three principal frontiers: with the imagery of dreams, with eidetic images, and with hallucinations. In marginal cases the most appropriate name is difficult to choose, though typical instances of all four classes of experience are fairly readily distinguishable.

Typical hypnagogic images may be more common than is generally realized (Leaning, 1925; McKellar and Simpson, 1954) although frequent occurrence, such as was reported by Maury (1948) in his own case seems rare. Visual hypnagogic images are experienced more often with closed than with open eyes,

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† It may be noted in passing, however, that Bexton, Heron and Scott (1954) have recently drawn attention to the similarity between hallucinations experimentally produced by sensory deprivation, and those of mescaline.

they are more often coloured than not, and their subject matter is almost infinitely varied. As illustrative description we may quote one subject who described them as "a series of images which pass across my field of vision from right to left as if projected from a magic lantern that is being rotated. I cannot hold them long and the pictures seem unrelated to each other." It is of interest to note that Eshner uses the same metaphor of "magic lantern" to describe his mescaline visions (Weir Mitchell, 1896).

The imagery of the hypnagogic state is of interest in several ways, apart from resemblances to mescaline phenomena. The visual, auditory and other images are reminiscent of certain types of hallucination with an apparent hysterical, toxic, or psychotic basis. They may be related to, or the occasion for, night terrors in children, and it is probable that in this field the importance of dreams and nightmares has been exaggerated and that of hypnagogic imagery underestimated. Hypnagogic experiences may be significant in the production of folklore, particularly as the subjects who report them are accepted as neither dreaming nor mad when the visions are seen or the voices heard. They may similarly enrich the content of a pre-existing psychosis and provide material for delusional interpretations, particularly in paranoid illnesses. They also appear on occasion to have provided source material for imaginative works of art.

HYPNAGOGIC AND Mescaline-INDUCED VISUAL EXPERIENCES

In considering similarities between experiences under mescaline and those of the hypnagogic state, we shall draw not only on our own data but also from the literature: the latter to anticipate the criticism of "effects of suggestion". The *visual* hypnagogic image is obviously of special interest in any comparison with mescaline's effects: as Havelock Ellis puts it, mescaline induces "mainly a saturnalia of the specific senses, and chiefly an orgy of vision" (1897, p. 1542). Moreover, visual imagery is probably most susceptible to precise description and analysis. The characteristics of hypnagogic visualizations will be examined and compared with the visions of mescaline under the following somewhat arbitrary headings: mode of presentation, quality, content and synaesthesia.

1. *Mode of Presentation*

Hypnagogic images appear and depart and the overall effect is not infrequently likened by the imager, as by a mescaline subject, to a magic lantern show with individual pictures coming into focus and then fading. Many introspective reports emphasize this quality, for example: "It seemed to be projected before me like a coloured film . . . It was quite unlike a mental image." Like mescaline visions they may be detected with closed eyes, or less frequently with open eyes. In sequence of presentation hypnagogic images resemble mescaline visions in that both tend to be disordered and inconsequential. It is as though the slides of the "magic lantern show" had been shuffled and presented in random order. Both types of imagery may, in this respect, be contrasted with the imagery of dreams, which tend to a more orderly succession. We have been able, on a number of occasions, to time several hypnagogic images. Some came and went in an instant, others remained a few minutes, but the majority—again like mescaline images—lasted a matter of one or two seconds.

A strongly characteristic feature of both mescaline and hypnagogic imagery is an apparent *autonomy*. As Weir Mitchell (1896) has noted, hypnagogic images resemble the images of mescaline in seeming to occur without, or even in defiance of, voluntary control. They tend to both "exist" and "behave" independently of the observer's other thoughts and perceptions and this is most

strikingly in evidence when, as is sometimes the case, they compete successfully with reality. William James (1892) among others stresses this autonomy "in the sense that all feeling of our own activity in producing them is lacking". A similar observation is contributed by the Rev. George Henslow—one of Galton's subjects who made a detailed study of his own hypnagogic images—who reported: "When the process is in full activity I feel as if I were a mere spectator at a diorama of a very eccentric kind, and in no way concerned with the getting up of the performance" (Galton, 1883, p. 117). The autonomy of the experiences was frequently noted by our own hypnagogic subjects, and commented on. We may compare such descriptions with what has been regularly noted by subjects under mescaline and particularly Lindemann and Clark's (1952, p. 565) description of the mescaline-intoxicated individual as "an interested spectator whose planned action is waived for the duration of the show". Our own mescaline subjects were repeatedly impressed by the autonomous character of their mescaline visualizations, and on occasion gave evidence of a kind of half-belief in the independent existence of the imagery: as one of them remarked "I could quite easily step back and it would still be there".

2. *Quality*

The characteristic of unusual *vividness* which both mescaline and hypnagogic images show, may first be noted. Ordinary memory and imagination imagery tends to be described as poor and shadowy by comparison. Warren (1934) in his definition describes hypnagogic images as "frequently of almost hallucinatory character". Freud (1900) and some other investigators, it may be noted, prefer the term "hallucination" to "image" to denote the experiences. This rather typical characteristic of vividness is well illustrated by one of our subjects who reported seeing a hypnagogic image of green cockatoos and bamboo trees: "I was dozing off and I suddenly saw it and distinctly heard it—a jungle sort of noise—bright sunlight and those birds waving up and down—green and brown, and vivid, vivid yellow." The quality of vividness which distinguishes the typical hypnagogic image from the imagery of ordinary thought and fantasy, is also characteristic of mescaline induced visions.

In the nature of their *colour* the typical mescaline and hypnagogic visualizations again seem to resemble each other closely. As has been frequently noted under mescaline, subjects very often report a variety of brilliant hues which surpass those of ordinary experience. As one of Prentiss and Morgan's (1895, p. 581) subjects reported "The colours were wonderful. They were the colours of the spectrum intensified as though bathed in the fiercest sunlight." Not infrequently hypnagogic images also appear as though sunlit, for example one of our subjects had the recurrent image of "a vivid view of hills and sea coast with sun glinting on the water, and heather on the hills". (This subject added that her hypnagogic images were always coloured.) Sometimes both mescaline and hypnagogic images appear to exhibit unusual colour quality of an exaggerated kind which even a term like "bright sunlight" does not fully convey. Lady Berkeley who, as one who painted a series of her own hypnagogic images, would have been particularly concerned with accurately observing such colour, uses terms like "liquid fire" and "strange luminosity" (Leaning, 1925). Leaning actually quotes Weir Mitchell's descriptions under mescaline to illustrate the qualities of colours imaged hypnagogically.

Hypnagogic visions commonly exhibit size changes in the imaged objects: both the *micropsia* and the *macropsia* to which Klüver (1942) has drawn attention in the case of mescaline. Thus one of our subjects reported recurrent

hypnagogic images "of people whom I have met at some time, but they always grow bigger and bigger until I cannot picture them, or fade away to a single point". Another reported seeing "people I know as larger or smaller than life size". Leaning (1925) suggests there is a tendency for hypnagogic images to approximate more closely to normal size as the subject passes from childhood to maturity, and cites Galton's (1883) subject who described a drift of great pink roses which she first saw when a child of nine, and which subsequently became "annually smaller, swifter, further off". One of our subjects under mescaline was impressed by the fact that hallucinatory red dots decreased in size as the drug wore off, and increased in size when he lapsed into a dreamy preoccupied state.

An immense *clarity of detail* is reported of some hypnagogic images. Thus, in describing his own hypnagogic visualizations Thomas (Leaning *et al.*, 1925a, p. 150) describes seeing "a white road and an avenue of trees, every detail—leaves, trunk, cart-ruts, pebbles—microscopically clear". Many individuals both in our own series and in the instances collected by Leaning emphasize this quality and report "detail so distinct even to obtrusiveness". Of this distinctness Leaning elsewhere (1925, p. 305) remarks: "Some hypnagogic subjects labour this (topic) in a way that suggests a super-distinctness, as it were microscopic clearness of detail, which is characteristic of the visions and independent of the native equipment for seeing." Again, similarity with mescaline-induced imagery may be noted: the characteristic of clarity of detail has been stressed by several mescaline investigators (e.g. Havelock Ellis, 1897). One of Guttman's subjects (1936, p. 212) reported a similar clarity of detail in his open-eyed mescaline visualizations: "The objects stood out more distinctly. The faces of the people around appeared to me more sharply outlined and more deeply furrowed than before."

3. *Content*

Relatively formless patterns which have been called "luminous dust", "*Eigenlicht*", or "idio-retinal sensations" can be detected by most—perhaps all individuals—on closing their eyes in a darkened room. These appear to be the subjective manifestations of retinal and other entoptic activity; they probably have some dependence upon after-sensations and upon the effects of tactile and other forms of inadequate stimulation of the eye. Such sensory effects may well constitute the raw material from which more structured visualizations can take place. As Havelock Ellis (1911, p. 31) states this theory: "The eye supplies entoptic glimmerings, and the brain acting on the suggestions received, superimposes mental pictures on these glimmerings." These experiences could hardly be called hypnagogic images, yet the difference is probably of degree only, and, as one of our subjects (who is a frequent imager) remarked: "The bits of light seem to merge into pictures sometimes". We would suggest that the relation which holds between these luminous dust experiences and hypnagogic images of the visual kind is probably very similar to that which holds between them and mescaline imagery.

Klüver (1942, p. 178) has noted that some or all of the "form constants", in terms of which he has analysed mescaline experiences (Klüver, 1928) also appear hypnagogically. *Patterns* of the kind so common under mescaline are probably rarer in hypnagogic visualizations. When they occur hypnagogically their description is very reminiscent of what might have been spoken by a mescaline subject. Examples of such hypnagogic patterns may be taken: "Most beautiful decorative patterns, finials, curves, spirals, leaves, blossoms" (Leaning,

1925). As illustration of this type of hypnagogic imagery reported by our own subjects we may quote: "all-over pattern of repeated design" and "lovely complicated patterns spread out like a carpet". As parallels from a rather typical kind of mescaline imagery we may instance Beringer's subject who saw flowers which wove themselves into the decorative pattern of a carpet, and Cairns, who saw knights wearing beautifully patterned cloaks (Marinesco, 1933).

Polyopia, whose frequency as a mescaline symptom has been stressed by Klüver (1928, 1942) may be described as a visualization which appears in a duplicated and re-duplicated form. That polyopia occurs hypnagogically as well as under mescaline has been noted by Klüver (1942, p. 183). As illustration of hypnagogic polyopia we may quote one of our subjects who reported the image: "Rupert Bear with an elephant sitting in a toy tank going up and down hills . . . a whole string of bears and elephants one behind the other like a string of sausages."

Faces are frequently seen hypnagogically and, in fact, the imagery has sometimes been called the "faces in the dark phenomenon". Such faces appear sometimes as elaborations of inanimate specks, and on occasion a part of the face is first perceived, for example an eye, and the rest added as a sort of concretized rationalization. It is of interest that such faces, though resembling pictures in their design and colour, may have a lifelike quality or may be described as "more vivid than nature, absolutely full of life and movement". Similar feelings of *heightened reality* attached to whatever one happens to be imaging, hallucinating or perceiving at the time, are not uncommon under mescaline. Hypnagogic faces and this accompanying sense of reality both find illustration in the following example: "Terrifying faces, one replacing the other. This happened quite often when I was younger . . . They seemed too vivid and too extraordinarily evil not to belong to something real, somewhere."

More complex types of hypnagogic visions include scenes and landscapes. Whereas the faces appear to range from the "indescribably beautiful" to the "grotesquely ugly", the scenes and landscapes are rarely other than pleasing. As illustration we may cite Miss Cunningham, who reported "beautiful leaping and running figures in gardens full of flowers" (Leaning *et al.*, 1925, p. 147). Similar scenes may be visualized under mescaline, for example, Guttman's subject who imaged "the surface of the earth . . . corrugated by three chains or rather massifs of snow-clad mountains" (Guttman, 1936, p. 208). Among other highly structured hypnagogic images are those of jumbled print. Leaning *et al.* (1925a) report one such subject who described the recurrent "hypnagogic image of a printed book which I try to read. I never succeed in getting more than about half a line and it is always the same kind of nonsense." We have observed similar imagery of "jumbled print" under mescaline and, as possibly a related phenomenon, images of numbers appearing upside down.

4. *Synaesthesia*

The phenomenon of synaesthesia so typical of mescaline intoxication seems rare hypnagogically but it does occur. It was not reported by any of our subjects, but Silberer (1909) gives several instances. We are indebted to Dr. E. H. Gombrich (1955) for a description of a hypnagogic image of a black scarf with red embroidery. The red colour was related by the subject to the warmth and contact of a hot water bottle and the black to the parts he couldn't feel; this might be classified as a hypnagogic synaesthesia of the visual-thermal type (Simpson and McKellar, 1955).

SOME AETIOLOGICAL FACTORS

Attention, practice and interest seem to affect the occurrence and content of hypnagogic imagery, and in this sense may be regarded as aetiological. It is as though some individuals can be "alerted" to notice their imagery. Thus many of our own subjects denied ever having had such an image, but within a few days reported visual or other images of the hypnagogic kind. The following remark is typical of this group: "They were there, but I'd never previously grasped the fact that they *were* there." On the other hand, close scrutiny may disrupt the image—a further point of similarity with mescaline visions. Leaning's subject, cited above, who visualized print hypnagogically, but who found that attempting to read it led to its disintegration, exemplifies this. This is comparable with the effect of close attention in abolishing hallucinatory movement under mescaline. As one of our subjects said of such movement "it is 'furtive' in the sense that it stops when you look *at* it".

Mescaline itself is of interest for its ability to alert the subject to hypnagogic experiences, and some of ours reported detecting "mescaline-like" visions in the hypnagogic state since having had the drug. In addition, mescaline and hypnagogic effects appear to summate, for during some of the experiments subjects quite frequently reported intensifications of their mescaline imagery before sleep.* Weir Mitchell's (1896) account of mescaline shows clearly that his visions increased in complexity and interest as he relaxed in a darkened room and almost fell asleep. We would suggest in the light of these various observations, that a sharp distinction between images which are "hypnagogic" and images which are "mescaline-induced" may, on occasion, be difficult to maintain.

THE IMAGERY AS CONCRETIZATION OF THOUGHT

In addition to the characteristics of imagery and perception as already discussed, in certain other respects the occurrences of the hypnagogic state resembles those of mescaline intoxication. These include depersonalization phenomena; alterations of the time sense; unexpected emotional changes; intellectual difficulties; quasi-delusional losses of insight; and most striking of all, changes in the body schema. We shall not be concerned to examine these, but will confine ourselves to some phenomena of thinking that may assist explanation of certain visual experiences.

Hypnagogic thinking shows a rather characteristic bias towards the concrete. As Silberer (1909, pp. 198-9) puts it: "The tired consciousness, not having at its disposal the energy necessary for normal thinking, switches to an easier form of functioning." A similar "marked tendency to think in visual images" under mescaline was noted by Mayer Gross (1951, p. 318). Guttman (1936, p. 213) makes the further point that such images may interfere with thought, and instances one of his subjects who reported "Each word I thought was connected with a picture. This hindered my thinking, as the concrete pictures held me." Incidents involving such interference with thought by vivid, intrusive imagery occurred very commonly in our mescaline series. Something very similar appears to happen with hypnagogic thinking when it is possible to observe this closely. To illustrate, one of our subjects when in the hypnagogic state and when experiencing hypnagogic images was asked to explain the proverb "Too many cooks spoil the broth". This she was unable to do, but she reported

* Only three instances of auditory hallucination were encountered in our series of mescaline experiments. On each occasion the experience occurred when the subject was settling down to sleep.

an immediate image of "little men in white overalls . . . there were two . . . two men". The image appeared to be not merely an interesting concretization—cooks in white overalls—but also a product of clang association: "Too many—two men." The early experiments of Silberer on hypnagogic thinking in himself provide further instances of this process of concretization. To illustrate, Silberer was lying on a couch and had set himself the problem of comparing the views of Kant and Schopenhauer concerning the nature of time: "In my drowsiness I was unable to maintain their ideas side by side . . . the futile effort to find the Kant record which was somehow misplaced in my mind suddenly represented itself to me—as I was lying there with my eyes closed as in a dream—as a perceptual symbol: I am asking a morose secretary for some information. He is leaning over his desk and disregards me entirely; he straightens up for a moment to give me an unfriendly and rejecting look. The vividness of the unexpected phenomenon surprised, indeed almost frightened me. I was impressed by the appropriateness of the unconsciously selected symbol" (Silberer, 1909, pp. 195–6). Again from Silberer (1909, p. 202): "My thought is: I am to improve a halting passage in an essay . . . I see myself planing a piece of wood."

The concept of "hypnagogic concretizations of thought" may help to explain certain kinds of image, notably those involving unusual and strange points of perspective of the type noted by Leaning (1925). We would suggest that these might well be interpreted as a visual portrayal of a concept rather than a recollection of what has actually been seen in the past. Thus the subject of Leaning's (1925, p. 335) visualized: "a section through earth, sea and air, the surface of the sea with ships on it, then a wall of waters, then the earth's globe like an orange cut down", and may well have been giving expression to a way of *thinking* about the globe. A further instance of this unusual type of perspective is provided by Professor Newbold who underwent an experience of apparently "flying, face downward, about 20 feet above the ground. It is always night, and I am following a road, trees, fences, fields, dimly seen along the roadside" (Leaning *et al.*, 1925a, p. 151). This may have been his visualization of a concept partly determined by his experience of motoring (as he suggests) but also partly by thinking of a road on a map. Yet again, the optically impossible clarity of detail of some hypnagogic images perhaps represents clarity and detailed treatment by thought rather than by perception.

CONCLUSION

To recapitulate, hypnagogic images and particularly those of a visual kind, resemble mescaline experiences in their mode of presentation, general quality and content: colour, vividness, clarity, autonomy, and so forth. Mescaline intoxication and the hypnagogic state may give rise to similar concretizations of thought. With both mescaline and hypnagogic images, as with dreams, personal interests together with possibly, deeper psychodynamics, seem to play a part in determining content. Alerted attention as opposed to close scrutiny seems to favour the occurrence of both mescaline and hypnagogic imagery. Parallels exist also in relation to the non-visual senses.

On the other hand, certain differences should be noted. Auditory hallucinations, so significant in the natural psychoses, occur commonly in the hypnagogic state and rarely under mescaline. The hypnagogic experience of "falling" does not appear to have any frequent counterpart in mescaline intoxication, whereas synaesthesias so characteristic of mescaline are rare in the hypnagogic state. Mescaline visions in their content seem more often to favour geometrical

patterns and inanimate objects, while hypnagogic images are more often of faces or landscapes. Movement of the images is probably more common in the case of mescaline. Such differences as these may be noted but, all in all, similarities are impressive. Such similarities would suggest a common principle—a principle which may assist us to understand the mode of production of the various manifestations of mescaline intoxication, and perhaps at some future date, of psychoses as encountered clinically.

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A CLINICAL TRIAL OF RESERPINE IN THE TREATMENT OF ANXIETY

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INTRODUCTION

ONE has to admit that the treatment of the mentally ill by psychological methods only leaves something to be desired, for even in the neuroses the long term results of psychotherapy are at times disappointing. Shorter methods of treatment, more economical of time and surer of outcome are constantly sought and, of course, there remains the very considerable problem of how to treat the not over-intelligent neurotic who can never hope to achieve profound self knowledge or insight.

The present investigation was suggested by the almost simultaneous appearance of two papers this year—one by Gloor (1954) containing a review of Hess's researches in diencephalic physiology, and the other by Plummer *et al.* (1954) describing the pharmacology of a newly available alkaloid reserpine which is extracted from the root of the plant *Rauwolfia serpentina*.

Reserpine has been used for some time by general physicians, and although reports indicate that its action in hypertension is mild yet side effects such as feeling of well being, relaxation of tension, calmness and tranquillity are frequently described. Livesay *et al.* (1954) using reserpine in a dosage of 2 mg. daily, which they consider the optimal dosage, report mild sedation without somnolence and a general sense of well being. They believe it to be superior to drugs such as phenobarbital in its ability to allay anxiety. Such sedative or quasi-sedative properties naturally attract the attention of the psychiatrist. Plummer notes that this state of quietude occurs in all laboratory animals, and other effects described by him referable to effects on the autonomic nervous system include miosis, bradycardia, hypotension, and augmentation of secretory and motor activity of the bowel. All these effects can be explained as decreased sympathetic preponderance and the site of action is postulated as being in the hypothalamus, for no other level in the nervous system could account for all the phenomenon. Now Gloor, interpreting Hess's findings in hypothalamic physiology, gives this picture of functional organizations there. Hess points out that sleep is not a state of inhibition, but is part of an actively reparative and resting type of behaviour. He has been able to produce sleep by actively stimulating certain areas in the anterior hypothalamus. Although most skeletal muscles are reduced in tone in sleep, yet the sphincter pupillae is contracted; the cat shows selective tone in flexor muscles when asleep—it curls up—and other animals show similar specificity in muscular tone when asleep, e.g. fowls sleep on one leg, horses can sleep standing. The rest of the musculature is, however, adynamic, and again using stimulation techniques Hess has been able to show that from closely related points in the anterior hypothalamus there occurs as well as inhibition of muscular tone a drop in blood pressure, a slowing of respiration, pupillary contraction, defaecation and micturition. These are all reactions which release tension by diminishing the capacity of the organism to produce physical effort. To this group of functions he has given the name endophylactic or trophotopic. Since in the posterior hypothalamus there exists a dynamogenous-ergotropic zone from which quite

opposite functions can be elicited, i.e. rise in blood pressure, pulse rate, rage, the fight and flight response, it becomes at least a possibility that the diencephalon is the place where somato-autonomic integration is finally achieved to produce a meaningful behaviour pattern. For example, in addition to the rage reaction, other complex acts can be brought about, e.g. the sniffing response, concerned with feeding and sexual activity, motor responses such as excessive walking about until the animal becomes listless and tired, and finally excessive and voracious indiscriminate eating—bulimia.

Purely from the behavioural point of view, therefore, a group of psychoneurotics, 35 in-patients and 5 out-patients at a neurosis centre were treated with reserpine, and an attempt was made to measure its effect upon anxiety and to interpret the results in relation to the above theory. They were all suffering from anxiety neurosis, anxiety hysteria or obsessional tension states. Pathological tension resembles excessive arousal in some ways, for example insomnia is a symptom very commonly experienced. Symptomatically therefore, many of the complaints of the neurotic might be due to over-activity of the dynamogenous zone. Cannon (1920) pointed out that anxiety can be looked upon as a state of preparedness for emergency. The investigation was therefore partly concerned with somato-autonomic response to stress. It is generally considered that the psychoneurotic is characterized by instability of various physiological systems and that this lability is particularly evident during stress. The experimental method adopted was based on the technique of Malmö and his co-workers who have made such valiant efforts to carry over laboratory work into the clinical field (Malmö *et al.*, 1948; Malmö and Shagass, 1949; Malmö, Shagass and Davis, 1950; Shagass, 1953).

EXPERIMENTAL METHOD AND TECHNIQUE

The now usual double blind technique was used, so that neither patient nor observer knew whether the tablet administered was a placebo or not. A group of 40 patients in all was treated, 20 receiving the drug and 20 the placebo. The treated group consisted of 8 females and 12 males with ages ranging from 17 to 65 with an average of 38.5. The control group was also fortuitously made up of 8 females and 12 males with an age range of 18 to 46, average 36. They were reasonably comparable groups and scores in Sidney Crown's Word Connection List (Crown, 1952) showed an almost equivalent degree of "neuroticism" in both groups (see Table III). Dosage to be effective has been generally supposed to be about 1 mg. per day. In this investigation the patients were given 1 mg. daily for the first week; 2 mg. daily for the second week; 3 mg. for the third week; and on the fourth week the dosage was dropped to 1 mg. daily. Previous reports had emphasized the cumulative action of the drug and the considerable time lag between administering it and noting its effects (Wilkins *et al.*, 1954). The patient was estimated for anxiety and tension at the start and at the end of four weeks' treatment.

An attempt was made to keep the measures as objective as possible. Therefore, as well as clinical evaluation, an anxiety symptom questionnaire was drawn up and the patients were specifically asked whether they suffered from insomnia, anorexia, restlessness, inability to concentrate, special phobias and obsessions, depressed moods, crying spells, feelings of panic, headaches, tremors, giddiness, palpitation, dyspnoea, urinary frequency, diarrhoea, vomiting, persistent feelings of tension and unremitting worry (each symptom being scored 0, $\frac{1}{2}$ or 1, maximum score = 18). Some physical signs in common clinical

usage were scored also—eye blinks, static ataxia, finger tremor, general restlessness. These were estimated visually by observation of the patient during interview and were rated 1–3 each for normal values, 4–5 for borderline subjects, and 6–8 for frankly abnormal findings (i.e. normal score 4–12, borderline maximal 18–20, over 20 definitely pathological). Information on “neuroticism” was obtained, as mentioned above from S. Crown’s Word Connection List administered before and at the end of the trial.

The physiological measurements were carried out on an Ediswan 6 channel electro-encephalograph, used as a modified polygraph, and the patient’s response to a mildly stressful situation was recorded and measured. The clearest correlation between degree of anxiety and degree of physiological disturbances under stress has been found in measurements of striate muscle activity, such as finger movement and neck muscle potentials (Malmo and Shagass, 1949). Sympathetic nerve fibres ending in muscle are believed to augment the tone. The apparatus was therefore arranged as follows. The patient sat in an arm chair in the upright posture. Channel 1 of the electro-encephalograph was used to record the E.E.G. from the right temporoparietal region and per cent. time alpha was measured. Channel 2 recorded the activities of the neck muscles—surface copper electrodes being used, one placed on cervical spine posteriorly and the other over the left sterno-mastoid. Channel 3 was used for the electro-cardiogram (E.C.G.), copper electrodes again being used on the palmar surface of each wrist. Channel 4 measured finger movements and alteration in tension of finger pressure—the hands were placed on a cross board with the fingers lightly resting on a carbon microphone. Channel 5 recorded respiratory movements—a belt of elastic webbing was applied to the upper chest with adjustable attachment and a carbon microphone was sewn into it in such a way that cellulose packing exerted varying pressure on the microphone with inspiration and expiration. This method, though not altogether satisfactory, was found to be effective enough in indicating respiratory disturbance in response to stimuli and this in fact was what was measured. The stress consisted of (i) intermittent flashing light from a Scophony stroboscope of 17 cycles per second, mounted on a metal arm a few inches from the patient’s face and (ii) a shrill whistle blast which, although the patient had been warned at the beginning of the test, almost always gave the startle response. After the patient had been installed in the apparatus he was reassured that he would feel no discomfort but that sometimes a light would flicker and sometimes he would hear a whistle. He was informed that this was a test to see how emotionally upset he was, and he was asked to co-operate by relaxing as completely as he could. Recording was continued for eleven minutes in all, paper speed being 3 cm. per second with a trace marker indicating one-second intervals. For the first three minutes the subject sat with the eyes closed, during the fourth and fifth minutes rhythmic photic stimulation was applied, the subject opening his eyes for 20 seconds and then closing the eyes for 20 seconds alternately during this time. For the sixth minute no stimulus was applied, but the whistle was sounded at the beginning of the seventh minute. These same stimuli were repeated during the eighth and ninth minutes, and at the beginning of the eleventh minute.

TREATMENT OF DATA

Symptom scores, scores of physical signs and Word Connection List were given to patients and controls before treatment began and after one month’s treatment. Physiological results were similarly obtained before and after

completion of treatment. The method of measuring the physiological tests was as follows:

(a) Per cent. time alpha. Recording paper was conveniently divided into ten-second strips. Any strip which showed a rhythm of 8–13 cycles per second present provided at least three consecutive diphasic excursions were present was considered as alpha present. The number of ten-second strips in which alpha appeared was then expressed as a percentage of total recording time.

(b) Muscle potentials and finger movements. Only degree of change could be measured, for individual variation is so great that various settings of sensitivities, time constants and filters had to be used. No reference to constant standards was therefore possible. Values were given to neck muscle potentials and finger movements on a scale varying from 1–4. 1—little or no pen excursion, 4—maximal pen excursions. Values during stimulation, i.e. during four minutes of rhythmic photic stimulation and for each half-minute after the whistle was sounded (i.e. for five minutes in all) were averaged as an “S” response. The remainder of the time, i.e. no stimulation yielded a resting (“R”) value. S-R was then taken as being a measure suitable for comparison between cases. Sometimes the S-R value was negative, but in the calculations the signs were ignored—displacement from the mean being the significant consideration. Preliminary investigation in normals yielded equivalent S and R values.

(c) Pulse rate. Degree of change was measured here also. S-R being taken as a measure of the degree to which the individual was distressed by the situation. Again negative signs were ignored and the result expressed as a percentage of the resting pulse rate, for individual variation was enormous.

(d) Respiratory disturbance. Owing to the rather simple equipment used only an upset in the smooth rhythm of breathing could be assessed with any certainty. The duration of the disturbance was measured in seconds up to a maximum of five seconds. After this point change in respiratory rate could not always be related to the stimulus. The average of the four readings was taken.

RESULTS

Clinical Results, Symptom Score, Physical Sign Score

The symptom score shows an improvement in the treated group as compared with the control group, and the difference just fails to be statistically significant (Table I). The score for the physical signs employed, however, does

TABLE I
Symptom Score

	Patient		Control	
	Pre.	Post.	Pre.	Post.
Mean	10.40	6.92	10.57	9.00
S.D.	1.330	4.103	2.751	3.664
Difference between Means		3.48		1.57
t		2.046		2.009

For N=20, Value of “t” corresponding to a probability of $P=0.05$ is 2.086.

not differentiate between the groups (Table II). An explanation of this fact will be offered later. The commonest and most obvious effect of the drug was to make the patients feel tired. They found it a considerable effort to initiate action of any kind—rather like Tennyson’s lotus eaters, but once launched into a task they were able to continue with it. For example all in-patients attended

occupational therapy throughout the trial, and the out-patients, who were all housewives, managed to do their jobs but all admitted that they were much more slow-moving and lethargic. As far as anxiety was concerned most expressed themselves as being more relaxed and less tense, but these are such vague terms that their value is doubtful—more reliance it was felt could be placed on the score in the symptom questionnaire. It will be seen that the control group also improved but the improvement of the treated group was considerably greater.

TABLE II
Physical Sign Score

	Patient		Control	
Mean	Pre.	Post.	Pre.	Post.
S.D.	16.40	14.8	13.50	12.50
Difference between Means	6.398	6.408	4.566	6.667
t		1.600		1.00
		2.846		2.651

Practically all expressed a feeling of detachment, a lessening of the sense of urgency and impatience, but since most patients knew the drug they were having and had learned from the lay press its reputed actions, it was felt that suggestion was operating too powerfully for the patients' introspection to be altogether trustworthy. One case out of the twenty became frankly euphoric but not in a socially unacceptable way. One similar instance of euphoria occurred in the control group. The impression was gained, and again the terminology is vague and unsatisfactory that as a result of taking the drug the individual showed a greater capacity for emotional contact with his environment, i.e. he became more "out going", less inhibited. Throughout the investigation, however, emphasis has been placed on group contrasts, individual reactions being interesting only as a pointer to further research.

Practically all the physical effects that had been reported in laboratory animals by the pharmacologists were noted, some unexpectedly so. For example, urinary frequency was a most notable feature and fifteen patients experienced nocturia to a moderate degree (i.e. two or more times per night). One patient who suffered from hypersomnia attacks and was suspected of being epileptic—the EEG was equivocal—had enuresis two or three times weekly while under treatment. This had only occurred on one occasion in the previous three months. This change in urinary habit was presumably due to increased tone in the bladder musculature since Gaunt *et al.* (1954) are quite certain that there is no interference with the formation of anti-diuretic hormone and no increase in urinary volume. Along with this increased tone of the bladder went increased tone of gut musculature also. Attacks of loose stools—not diarrhoea—occurred in two patients, and ten of the others noted that elimination by the lower bowel was more active. No change in bowel habits occurred among the controls. Eighteen of the treated group remarked with some surprise that their appetites were improved, some even waking up at night because of hunger. This had not been foreseen nor had the accompanying weight increase been expected, so that unfortunately no records of weight fluctuations were kept. However, it seems clear that most gained a few pounds and one man put on eight pounds in the month. The control group showed nothing equivalent.

Another regularly occurring phenomenon was the extent to which the patients dreamed. Fourteen experienced a marked increase in the incidence of dreams. The dreams were of a superficial, non-significant type—at least in

their manifest content and were in almost every case concerned with contemporaneous events and day to day occurrences. In only one case was there a profound emotional accompaniment. This man was a very tense obsessional paranoid, much afraid of his own aggression. He was on the border-line of psychosis and his clinical condition did not improve with the treatment.

As far as actual sleeping and sedation were concerned the depth of sleep obtained was not profound and the individuals quite easily roused. In one case the sleep rhythm was actually interfered with and he woke up repeatedly. Seven individuals required additional sedation, but all had been accustomed to barbiturates for years. However, in two cases with relatively severe barbiturate habituation the nightly sedative was able to be reduced to less than half the accustomed dosage and all day time sedation was discontinued. On waking up from sleep, however, most complained of a marked disinclination to get up. This was probably due more to the hypotonia than to any centrally acting anaesthetic like effect. In every case miosis was present but passed quite unnoticed by the patient.

Side effects also included nasal stuffiness—but only four complained of it to an extent that required treatment. Antihistamine nasal drops soon afforded symptomatic relief. Such is the extent of nasal and paranasal infection and allergy in this country that every individual whether in the treated or control group in answer to direct questioning gave indications of some degree of nasal stuffiness. Two other effects were noted, though they have no obvious clinical significance *per se*. In common with other skeletal musculature the facial muscles were relaxed so that the facies was rather sleepy and expressionless. Actually this was quite a reliable way of distinguishing between treated and control groups. In addition there was usually vasoconstriction of skin vessels and pallor and a heightened sensitivity to cold. At the least sign of chill in the atmosphere those receiving the drug would shiver and shake quite perceptibly. This was considered due to the hypothermic effect of reserpine and interference with the heat regulating mechanism.

Word Connection List

This is an easily applied modern form of the old word association test of Jung. It was designed by Crown and he gives norms and validations. Normal groups score $6.8^{+}4.1$ up to $13.9^{+}6.6$ and he altered his original cutting score of 8 to $9.9^{+}6.1$. Neurotics score much higher, e.g. hysterics $16.7^{+}7.2$ and

TABLE III
Crown's Word Connection List

	Patient		Control	
	Pre.	Post.	Pre.	Post.
Mean	15.20	13.15	15.00	13.70
S.D.	6.939	7.538	5.762	6.717
Difference between Means	2.05		1.30	
t	4.190		4.515	

anxiety states $14.6^{+}6.7$. The results here obtained show that treatment and control groups are quite well matched for the factor of neuroticism, but exhibition of reserpine fails to bring about any significant difference between treated and control groups—both showing significant improvement (see Table III).

Physiological Tests of Anxiety

Neck muscle potentials and finger movements. Proprioceptive sensations from muscle tone are important elements in the stream of consciousness and mental and emotional activity always involve a motor element: in short every psychic process has a neural correlate. This close correlation between muscular tensions and psychological tension has long been recognized and the case has been powerfully stated by Jacobsen in a classical monograph (Jacobsen, 1938). Recently using new electro-myographic techniques other investigators have re-emphasized the roles of the skeletal muscular system and have even made the plea that in view of the confusion that surrounds the usage of the clinical term "tension", it might well be reserved for cases showing increased tonus (Sainsbury and Gibson, 1954). Now a muscle which is under slightly increased constant stretch is much more likely to over-react to stimulation than it would do were it relaxed. This is a commonplace to every clinician using a tendon hammer. The psychoneurotic, however, with his anxiety ready to attach itself to everyday life situations inappropriately shows an impaired capacity to control or inhibit motor reactions under stress, so that in such conditions the excessive "preparedness" will be carried over into overt action more readily. It is well known that in neurotics the performance IQ's are less than the verbal IQ's. By measuring the degree of response to stimulation in a muscle information may be gained as to its resting state. From the therapeutic point of view, therefore, if treatment is effective the excessive purposeless tension in the test situation should be diminished, and the stimulation and resting values should

TABLE IV
Neck Muscle Potentials

	Patient		Control	
	Pre.	Post.	Pre.	Post.
Mean	9.00	3.90	10.98	8.23
S.D.	6.111	2.922	7.650	6.724
Difference between Means	5.10		2.75	
t	2.016		0.642	

TABLE V
Finger Movements

	Patient		Control	
	Pre.	Post.	Pre.	Post.
Mean	12.45	6.35	6.40	5.80
S.D.	9.340	4.984	6.045	3.707
Difference between Means	6.10		0.60	
t	1.657		1.397	

approximate, and ideally be equal. Although recording was only led off from one muscle group (the left sternomastoid), changes in this area have been shown to be reliably associated with changes in other areas of the body (Malmo and Shagass, 1949; Sainsbury and Gibson, 1954). Reference to Tables IV and V, shows that the improvement in both tests was satisfactory; there was a difference between treated and control groups but the difference was not significant.

Blood Pressure and Pulse Rate

Reference to Tables VI, VII and VIII shows that blood pressure—calculated

as Mean Arterial Blood Pressure (MABP=Diastolic pressure plus one-third of the pulse pressure) was considerably reduced and the pulse rate even more markedly so, so that an effective anti-sympathetic level of dosage can be said to have been attained. However, the response of the blood pressure to stress procedure was still elicited. There is apparently no interference with the

TABLE VI
Blood Pressure

	Patient				Control			
	Pre.		Post.		Pre.		Post.	
	a	b	c	d	a	b	c	d
Mean	106.55	109.45	100.10	100.55	101.00	102.10	100.30	99.35
S.D.	10.610	12.710	11.950	10.830	10.932	10.327	10.860	10.742

a=MABP before test } before treatment
 b=MABP after test }
 c=MABP before test } after treatment
 d=MABP after test }

TABLE VII
Resting Pulse Rate

	Patient		Control	
	Pre.	Post.	Pre.	Post.
	83.30	65.85	80.85	77.85
Mean	14.751	12.694	18.135	14.321
S.D.				
Difference between Means		17.45		3.00
t		4.582		3.626

TABLE VIII
Pulse rate alterations

	Patient		Control	
	Pre.	Post.	Pre.	Post.
	2.82	2.69	2.69	2.10
Mean	2.482	2.378	1.786	1.679
S.D.				
Difference between Means		0.13		0.89
t		1.353		0.980

emergency reactions of the body. Comparable results were obtained with the pulse rate. These findings were unexpectedly adverse, since the drug acts powerfully on the cardiovascular system, and it seemed reasonable to anticipate more stable conditions there. But other investigators have found that pulse rate alterations and blood pressure variations could not be shown to correlate reliably with level of anxiety. In this connection Ax (1953) explains the phenomenon in the general hypothesis that there is marked uniqueness in physiological expression of emotions, i.e. there are "cardiovascular" types of patients in whom emotional upset would be reflected in alterations in this system and not necessarily in other systems.

Nevertheless it is implicit in all psychological literature that a fast pulse is a concomitant of anxiety, so a slower resting pulse rate is at least a straw in the wind suggesting a lessened state of fear. The James-Lange theory has not

been finally refuted yet. Actually two of the treated patients had minor mishaps believed to be due to the hypotensive effects of the drug. Circumstances were exactly parallel. On the second night after commencement of treatment the patient got out of bed to pass urine, became giddy and fell down striking his head and causing abrasions of the scalp. The other patient did the same thing on the third night after commencing treatment. Next morning the blood pressure was not found to be profoundly depressed and treatment was not interrupted. Some kind of accommodation and adjustment to the altered internal environment must have occurred thereafter, for in neither case was the incident repeated.

Electro-encephalogram

The alpha rhythm is the rhythm of rest and is best seen in the relaxed subject (Hill, 1950). The relationship of this rhythm to emotional factors remains unsolved, but there are several indications that in heightened emotional states the amount of the alpha rhythm is reduced. Psychopathological tension states resemble excessive arousal in some ways, e.g. insomnia, and some neurophysiologists believe that this over awareness is due to centrencephalic reticular circuits interfering with homeostatic mechanisms existing between thalamus and cortex. Ulett (1953) reviews the evidence that poor alpha activity and the presence of slow and fast rhythms in the resting EEG are predominant

TABLE IX
E.E.G. Percentage Time Alpha

	Patient		Control	
	Pre.	Post.	Pre.	Post.
Mean	63·90	69·45	44·60	54·40
S.D.	11·630	12·490	13·545	14·172
Difference between Means	5·55		9·80	
t	1·148		0·591	

among psychoneurotic and anxiety-prone individuals. In counting per cent. time alpha as a function of tension states it is noteworthy that Davis (1941) found that in 400 “presumably normal” and “average” individuals alpha was dominant for 70 to 80 per cent. of the time. Table IX shows that the improvement made by the patient group was greater than that made by the control group but the difference was not significant. No specific changes characteristic of reserpine were found in the EEG.

Respiratory disturbance or irregularity has been found to be a more reliable measure of anxiety than respiratory deviations, perhaps owing to the startle effect. Malmo and Shagass (1949) have found a very close resemblance between curves of finger movement and respiratory irregularity in stress in patients suffering from anxiety. It was expected, therefore, that there would be some reduction in the figures for this test in the treatment group. However, the performance of both groups shows deterioration. This would seem to indicate that at the second time of testing, all patients, treated and control, were sensitized in this particular system, and that respiratory release is characteristic of psychological “set”. It seems likely too that reserpine, being a parasympathetic stimulator, causes a certain reduction in vital capacity and a tendency towards bronchospasm by vagal activation. In addition the nasal obstruction probably places an additional burden on respiratory function. No florid cases of asthma occurred, but one patient who suffered from turbinate

congestion most severely was noted to be using his accessory muscles of respiration at rest. He was a young athletic man, there was no history of lung or heart disease and auscultation revealed a moderate degree of bronchospasm,

TABLE X
Respiratory Disturbance

	Patient		Control	
	Pre.	Post.	Pre.	Post.
Mean	1.48	1.74	1.48	2.03
S.D.	1.350	0.902	1.240	1.607
Difference between Means		0.26		0.55
t		1.924		1.808

though the patient never complained of acute respiratory embarrassment. Along with four other patients he protested that he became short of breath on climbing stairs, but they blamed this on the tired feelings which all who took the drug experienced (see Table X).

To sum up—of the ten tests applied in an attempt to estimate anxiety level, none differentiated significantly between treated and control groups. Eight were suggestive of improvement (symptom score, sign score, blood-pressure response, pulse rate, pulse rate variability, per cent. time alpha, neck muscle potentials, finger movements) and two very closely approached a level of statistical significance (symptom score and neck muscle potential). One test suggested that the control group had improved more than the treated group and one test showed a deterioration in both groups. With regard to the failure of the clinical physical signs (eye tremor, finger tremor, static ataxia and general restlessness) to differ significantly, this seemed to be due to hypotonia and mild inco-ordination such as is seen in a state of great fatigue. The figures for general restlessness alone show improvement after treatment, but this tendency is offset by the increase in tremor. Vakil reported tremor as an unpleasant side effect in a small proportion of cases.

The overall picture of lessened anxiety is, however, reasonably clear and suggestive. On clinical grounds and judgment 14 of the 20 were improved, 8 markedly so, 5 were unchanged and 1 deteriorated—a rather gross “hysteric”, a middle aged man, passed over into a state of schizophrenic delusion of bodily change, complaining, perhaps significantly, that no air would go into his lungs. Eight have been discharged from treatment. Three expressed themselves as finding the tablets unpleasant to take because of lassitude and mild depression.

In the control group 2 believed that they were much improved, 6 slightly improved and 11 were unchanged. Four of the control group have left hospital. One became much worse, developing extreme agitation and ambivalence over every trifling act of daily life, expressed open hostility to the tablets and could only be persuaded to complete the course with difficulty. He became much better when the placebo was stopped.

Discussion—Rationale of Reserpine Treatment

Much has been said previously emphasizing the somatic concomitants of anxiety. Here is a drug which will reliably reduce these manifestations in a certain number of people. Peripherally, therefore, its action is demonstrable and satisfactory to the practitioner applying the treatment. If a patient presents with anxiety symptoms indicating over-activity of the sympathetic nervous

system, then the probability is that reserpine will relieve some of his symptoms and there will be behavioural improvement. It is not suggested for a moment that this is more than just an introduction and an adjunct to psychotherapy which must still remain the supreme therapeutic weapon. However, even at the behavioural level it may be that salutary effects will extend to other parts of the personality. It is quite remarkable that successful methods of physical therapy show three very nearly constant findings—alteration in appetite, sleep and motor activity. This is clearly so with insulin and apparently also with cortisone (Fox and Gifford, 1953). Now physical therapy might well be satisfied with securing behavioural improvements in this way, and indeed this attitude is implicit in the operations of leucotomy and lobotomy where the aim is to free the diencephalon from the noxious effects of the cortex. There is a case for this in more purely psychological terms. Let us say that certain types of neurotic illness are characterized by disturbance of primitive functions, like sleeping and eating. Even if these are the result of disharmony in other parts of the personality, if the sufferer is to be cured it is entirely relevant to restore these elemental functions, by artificial means if necessary. "Where an anxiety state continues for some time the physiological upset caused often leads to some degree of hypochondriasis, to bodily preoccupation and to a fear of organic illness" (Mayer-Gross *et al.*, 1954). If faulty functioning can become learned behaviour, then so can satisfactory functioning, and with each execution and reinforcement the good habits become self perpetuating. Habit is a potent psychological weapon and Allport (1938) considers it to be a basic principle of the psychology of personality—the functional autonomy of habit. Robert Louis Stevenson in order to become a proficient writer, "played the sedulous ape to Hazlitt", and in related literary-philosophical fields Aldous Huxley with the Holy Face of Lucca lends support to the dogma that self-righteousness is a step along the road to true righteousness. Dynamic psychologists do not hesitate to explain the higher nervous activity of modern man in terms of his primitive and archaic forebears. These concepts were developed ideologically and intuitively, but we are now possessed of an adequate body of knowledge to postulate an anatomo-physiological substrate to these theories that the various levels of the brain are linked materially as well as in fancy. Furthermore cybernetics has made us familiar with servomechanisms and the mutual interdependence of related circuits. It seems feasible, therefore, that archaic and primitive behaviour patterns and functions may exert a feedback effect on higher levels of nervous activity to an extent not realized. Hughlings Jackson's hypothesis of the hierarchy of neural centres and his rigid dualism for a long time obscured the fact that there was not only one-way traffic in a "downward" direction between cortex and subcortex, but the work of Jasper (1949) has demonstrated that there is effective two-way traffic between the thalamus and many parts of the cortex of the hemispheres. The importance of the diencephalon has been further emphasized by recent demonstrations of very close structural and functional linkage between the hypothalamus and the rhinencephalon or visceral brain (McLean, 1949). This region of the brain is at present in the very forefront of psychiatric thinking as the possible integrator of emotion, and the hypothalamus is the pathway through which emotion is converted into affective behaviour (Mayer-Gross *et al.*, 1954). Such behaviour reveals traits and qualities with which personality is intimately bound.

The objection has been raised that reserpine is just another sedative. Even if it were so sedatives are certainly necessary on some occasions and the search for effective and satisfactory drugs of sedation goes on. Lately certain grave

dissatisfactions with the barbiturates have been expressed (*Lancet*, 1954). Addiction is a reality and a pressing problem. Syndromes are described as chronic barbiturate poisoning, and overdosage has become almost the commonest method of suicide. The action of the drug here being investigated is entirely different in every way. There is no anaesthetic-like effect and there is a considerable time-lag before any results are noted. It does not, therefore, commend itself to the neurotic patient with the same immediacy as does a barbiturate. The depth of sleep obtained is not profound, and there is apparently a wide margin of safety. Vakil (1949) having treated several thousand cases can vouch for its non-toxicity with confidence. He has not come across a single fatality from the administration of this preparation. Doyle and Smith (1954) and Douthwaite (1954) report unpleasant side effects such as nasal obstruction, excessive fatigue, sleepiness, dizziness and depression, but this was in a dosage range of 12–16 mg. daily for severe hypertension. The only dangerous effect occurring in the literature so far is one case reported by Smith and Smith (1954) who found alarming angina pectoris occurring in a man of 43 with moderate hypertension. Symptoms came on immediately after taking small doses of reserpine (serpasil) 0.125 mg. On the other hand Plummer (1954) has heard of a case of a 20-month old boy weighing 32 lb. who accidentally swallowed 200 mg. There was a non-specific toxic reaction, with pyrexia and fast pulse for the first 24 hours, and he slept most of the time but could be wakened for food and drink. He was lethargic for six days afterwards, but very thorough biochemical examinations carried out regularly up to two months after the incident showed no significant abnormalities, and the child remained perfectly well.

Although the intimate action of the barbiturates at the cell level remains a matter for speculation, yet Greville and Heppenstall (1950) conclude that they act as a blocking agent in the many internuncial relays of the brain stem reticular activating system of Moruzzi and Magoun. There occurs in fact a thalamic deafferentation so that the organism is deprived of contact with the environment to some extent. Characteristically fast rhythms of 14–20 cycles per second are seen in frontal and central areas of the electro-encephalogram after barbiturate administration. Reserpine is believed to act by stimulating or potentiating the most rostral of the centres for autonomic activity and so far no specific EEG changes have been attributed to it.

SUMMARY

The claim that reserpine diminishes anxiety has been investigated. A group of 20 patients suffering from anxiety and tension was given one month's treatment, a comparable group of another 20 being used as a control.

Of ten objective tests of anxiety applied, none showed sufficient improvement to be statistically significant as between the groups but two approached the level of significance, and six more were suggestive of improvement.

Clinical findings have also been described, and the effects of reserpine compared with other physical agents in use in psychiatry. A probable mode of action has been discussed in the light of present day neurophysiological knowledge. The action of reserpine has been compared and contrasted with the action of the barbiturates.

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INTRAVENOUS ACETYLCHOLINE THERAPY IN NEUROSIS

A CONTROLLED CLINICAL TRIAL

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It is now several years since acetylcholine was first administered intramuscularly in the symptomatic treatment of anxiety, on the theory that anxiety was sympathicotonic in nature and could be counteracted by the vagotonic action of acetylcholine. Unfortunately decomposition of acetylcholine is so rapid that there is little time for this action to be effective, and the majority of investigators believe that it has no effect, or at least a momentary one, when given either subcutaneously or intramuscularly. Maxwell Jones (1936) used carbachol, a drug with a similar but more prolonged action than acetylcholine to treat six patients with anxiety neurosis. He was able to report relief from the psychic and somatic symptoms of anxiety in all cases but unfortunately, following withdrawal of the drug, they tended to relapse. An entirely different rationale led Tomasson (1936) to claim both alleviation and shortening of the duration of attacks of mania in manic depressive psychotics using a combined ephedrine and acetylcholine treatment.

The first reports of the intravenous use of acetylcholine in the treatment of psychiatric patients were by Fiamberti (1939). He treated early cases of schizophrenia using the bromide, Pragmoline, which was given intravenously in doses of 600 mg. This was injected with sufficient rapidity to obtain loss of consciousness with a convulsion, preceded by phenomena corresponding to intense parasympathetic stimulation. Fiamberti in further publications on this form of treatment (1947, 1950) has claimed a recovery rate of up to 80 per cent. Despite this the treatment has gained little support in the English literature, perhaps largely because of adverse reports by Harris and Pacella (1943) who treated eight patients without any benefit, and by Cohen *et al.* (1944) who found no therapeutic benefit in eight of eleven schizophrenic patients and only slight and moderate improvement in two others. Their last patient underwent a dramatic remission, but only after an alarming episode in which he was pulseless for such long periods that he was considered probably dead. They conjectured that the remission was a consequence of organic cerebral changes resulting from prolonged hypoxia rather than a specific drug effect, and believed that the margin of safety was extremely slight. In contrast to this view, Poort and Stigaard (1944) found that doses of acetylcholine up to 1 g. could be injected intravenously with safety. Other reports on various aspects of the method have been published by Borgarello (1939), Kulcsar and Lajtavari (1940), Sandri (1940), Ali (1940), Ferrio (1942), Stigaard (1944), Demetro (1945), Schaeffer (1947), Sacristan Hernandez de Tejada (1947), Alexandre and Almeida (1951) and Sogliani (1951).

The modified form of intravenous therapy which has found popularity in the past three years was introduced in Spain by Lopez Ibor and reported in 1950 and 1952, when he claimed it to be of value in the treatment of certain types of anxiety neurosis. Sargant (1952) developed the method in England and there have been subsequent reports by Maclay (1953) and Phillips and Hutchinson (1954) who described their results in 211 patients, the largest series to date. The authors have been carrying out this form of treatment with out-patients since 1952 and our results in 55 cases are summarized below (Table I).

TABLE I

Results of Acetylcholine Therapy

	Total	Ac. Anx.	Chr. Ten.	Som. Anx.	Anx. Dep.	Anx. Hys.	Ob. Neur.	Psycop.
I Symptom Free..	14 27%	9	1	2	2			
II Improved ..	17 33%	7	5	1		4		
III No change ..	15 29%	2	2			5	4	2
IV Worse ..	6 11%				1	4		1
V Refused ..	3			1		2		
Total ..	55	18	8	4	3	15	4	3

As will be seen, though our series is smaller, our results are comparable with those obtained by other workers. In the early stages we were most encouraged by several satisfactory responses and in particular by one patient with phobic anxiety and tension, who made a complete recovery though he had previously failed to improve with intensive and varied treatment. However, as time went on we came to question whether these results were a specific consequence of treatment with acetylcholine or more generally of the total therapeutic situation. It might be argued that our figures as well as those from the literature which reports a recovery rate of 60 per cent. (Lopez Ibor, 1952) and an improvement rate of 45 per cent. (Sargant, 1952) or, in the most favourable group, 70 per cent. (Phillips and Hutchinson, 1954) were sufficient evidence of the efficacy of the treatment. Unfortunately, this need not imply a specific action of the drug. From the undoubted but entirely non-specific successes of the Weir Mitchell routine, the history of the treatment of neurosis is one of many kinds of therapy at present producing numerous cures but later showing gradually diminishing results as their rationale came to be questioned and they were administered with less enthusiasm. One does not have to search far through the contemporary literature in order to find numerous and diverse treatments for which improvement rates of around 60 per cent. are claimed and one cannot escape the conclusion that in many cases it is the regime rather than the specific therapeutic agent which produces the result. Unfortunately, all too little is known not only of the natural history of the neuroses but also of what results may be anticipated from energetic therapy with essentially inert substances, and, when neurotic case material is broken down into more homogeneous clinical groups, this is even more the case.

It therefore seemed to us that before speculating on the possible mode of action of acetylcholine, and certainly before embarking on complex physiological and pharmacodynamic research, it was essential to provide a conclusive answer to the question, does acetylcholine have any specific therapeutic effect at all? We did not feel that any of the figures available permitted a satisfactory answer. The only comparison of treated with untreated cases is that made by Lopez Ibor (1952). Unfortunately, those constituting his untreated group represent patients who had refused treatment. This in itself would be quite sufficient to make them entirely unacceptable as controls, but in any case they did not go through a similar therapeutic process, and must be excluded on this ground also. He mentions having used intravenous ammonium chloride, picrotoxin, and nicotinic acid, the first of which was giving encouraging results, but while these cases might provide rather more satisfactory controls, no figures are given. We therefore determined to conduct a blind controlled study which forms the main material of the present paper.

DESIGN OF THE EXPERIMENT

We were anxious to arrange our trial in such a fashion that two similar groups of patients should pass through a therapeutic programme identical in all respects except for the critical one of having received or not received acetylcholine.

In order to give some idea of the therapeutic setting it should be explained that it is our custom to carry out acetylcholine therapy at a mixed out-patient clinic where patients are attending not only for this but also for E.C.T. and for Meduna type carbon dioxide treatment. There is a common large waiting hall and a single treatment room suitably divided by movable screens into 15 or more cubicles. The clinic is an exceptionally busy one, a total of 30 or more patients being treated in a two-hour period. This arrangement means that while the treatment is conducted in private there is a good deal of social mixing both before and after treatment, and the presence of a high proportion of E.C.T. patients, most of whom are deriving obvious benefit, results in high group morale and a great sense of therapeutic optimism.

Cases were selected exclusively by one of us according to predetermined criteria discussed below. They were then referred to the out-patient clinic where the other was responsible for carrying out the treatment. The only two members of the clinic staff aware that a therapeutic trial was being conducted were the one of us responsible and the sister in charge of the clinic. Selected cases were randomly divided into a treated and control group. It was decided to give the control group an identical quantity of distilled water and this, as well as the acetylcholine, was prepared by the sister in charge of the clinic. The loaded syringe was then brought to the appropriate cubicle by an assisting staff nurse who was not aware that a trial was being conducted, and sister, who of necessity knew which cases were controls, remained entirely in the background supervising other aspects of clinic work. In this way when a patient attended for his first treatment the one of us responsible for giving the injection did not know whether acetylcholine or distilled water was being given and the staff nurse assisting did not know that there was any possibility of the injection being inert. Naturally it very soon became evident to the operator which substance was being used, but we sought in this way to avoid any suggestion that unconscious differences in the mode of presentation at the critical first interview should play a significant part.

It was our practice to give a standard introductory explanation. This would point out that the patient would be expected to attend twice weekly for a period of not less than ten or twelve weeks and that on each occasion he would receive an injection. This injection might or might not be followed by certain sensations. If these did occur they would consist of a tight sensation of the chest, involuntary coughing, a flushing of the face, watering of the eyes, possibly palpitation and even a momentary sensation of dizziness. It was, however, emphasized that the occurrence or otherwise of these sensations was in no way related to a satisfactory response which could be expected as the treatment progressed. This was

The United Birmingham Hospitals

THE MIDLAND NERVE HOSPITAL

Name.....Age.....Sex.....
Reg. No.Diagnosis.....
Height.....Weight.....

ACETYL CHOLINE THERAPY

CASE DATA

Previous Neurotic Manifestations In Childhood ☐ In Adult Life ☐
Employment Record Stable ☐ Unstable ☐
Relevant Environmental Stress (Specify)
Previous Personality (Specify)
Intellectual Status Below Average ☐ Average ☐ Above Average ☐

Present Illness

Duration Years ☐ Months ☐
Severity Mild ☐ Moderate ☐ Severe ☐
Course Progressive ☐ Steady ☐ Cyclical ☐

Main Presenting Symptoms

Other Observations

Response to Treatment

Progress on Review

Date	

FIG. 1

also the explanation given to the staff nurse assistant. After the first visit further reassurance and encouragement was studiously avoided as, by this time, the operator would know to which group the patient belonged. Assessment of response was carried out solely by the original selector who reviewed patients at four-weekly intervals. He was kept entirely unaware of which patients were controls and was careful to avoid asking questions concerning the immediate reaction to treatment which might provide a clue. The illustrated pro-forma was used to record essential clinical data at the time of the first interview and subsequent comparable assessments of progress (Fig. 1).

Two main criticisms of our technique are anticipated. The first is the familiar one that it is fallacious to compare the responses of two different groups since individual differences are too great. In attempting to overcome this difficulty we preferred to accept an approximately homogeneous clinical group in the first place and then divide it on a random basis, rather than adopt the method of pairing. As will be seen from the figures below our two groups turned out to be comparable in many particulars (Table II). The more valid objection

TABLE II
Comparison of Treated and Control Groups

Factor								Treated	Control
Total	..	..	..	..	..	..	18	18	
Age	..	..	Minimum	..	..	..	18	22	
			Average	..	..	..	31	33	
			Maximum	..	..	..	44	46	
Sex	..	..	Male	..	..	..	11	9	
			Female	..	..	..	7	9	
Neurotic traits	..	..	Childhood	..	..	..	5	6	
			Adult	..	..	..	9	6	
Personality noted as	..	..	Over anxious	..	..	..	7	5	
			Obsessive	..	..	..	7	9	
			Hysterical	..	..	..	1	2	
			Inadequate	..	..	..			
Intelligence	..	..	Below average	..	..	..			
			Average	..	..	..	14	12	
			Above average	..	..	..	4	6	
Work record	..	..	Stable	..	..	..	18	16	
			Unstable	..	..	..		2	
Environmental problem			..	..	..	..	8	6	
Duration of illness	..	..	Minimum	..	..	..	0·7	0·5	
			Average	..	..	..	3·9	3·2	
			Maximum	..	..	..	10·0	12·0	
Pattern of illness	..	..	Phasic	..	..	..	7	9	
			Non-phasic	..	..	..	11	9	
Severity of Illness	..	..	Moderate	..	..	..	15	13	
			Severe	..	..	..	3	5	
Diagnostic Group	..	..	Acute anxiety attacks	..	..	..	5	6	
			Chronic tension	..	..	..	5	3	
			Somatic anxiety	..	..	..	2	4	
			Anxiety depression	..	..	..	3	1	
			Anxiety hysteria	..	..	..	3	4	
Average number of treatments				..	..	..	25·9	25·3	

concerns the very real difference in subjective experience of the two groups. Such could perhaps be held responsible for any significant differences observed but clearly would not invalidate a result which demonstrated no significant difference in the responses of the treated and control series.

THE SELECTION OF PATIENTS FOR THE TRIAL

The initial claims for this form of treatment were made by Lopez Ibor (1952) in a group which he described as "Anxiety Timopathy". By this term he implied an illness, endogenous in origin, which would include a majority of anxiety neuroses, many obsessive neuroses and some other cases scattered in various nosological groupings. The characteristic symptom was unmotivated anxiety which he termed "Vital anxiety" and compared in some respects to the unmotivated depression of a depressive psychosis. A second important feature of the cases in this group was their phasic character and on these grounds he believed them to have a biological basis independent of the diverse external or internal events in the individual history. He suggested that the mechanism involved was most probably diencephalic and it was in the search for vegetative stimulants of the diencephalon that he came to try, amongst other substances, the effects of acetylcholine. Sargent (1952), after using the treatment on a random sample of anxious and hysterical patients, concluded that it was of no greater value in hysteria than any other new suggestive treatment. Nor did he find it particularly helpful in the syndrome of anxiety hysteria which he defined as being characterized by phobic and anxiety symptoms in the setting of an immature personality and an asthenic habitus. His satisfactory results were reported in what he described as severe tension or phobic states in mildly obsessive personalities. Our own experience largely coincided with these views. Our best results had been obtained in patients of good if somewhat driving personalities, who usually maintained a considerable degree of objective efficiency despite great subjective distress, which often expressed itself in terms of acute phobic anxiety attacks or chronic tension. At that time the report of Phillips and Hutchinson (1954) was not available to us, but it would appear to confirm in greater detail Sargent's (1952) original impressions.

In selecting patients for our trial, we were anxious not to restrict our group too narrowly, but clearly it was desirable to exclude patients who were unlikely to respond. Schizophrenia, organic reactions, manic depressive psychoses, endogenous depressions and psychopathic states, were all made absolute contraindications. We also excluded rigid obsessional neurotics since our experience had confirmed that these were not benefited. The remaining cases, which fall almost exclusively into the psychoneurotic group, constellate into predominantly hysterical and predominantly anxiety reactions. It was chiefly from the second group that we selected our patients for the trial, and we regarded as positive indications for selection, acute anxiety attacks, simple unelaborated somatic anxiety symptoms, the phobic and obsessive expression of anxiety and chronic anxiety and tension. A neurotic depressive admixture was not a basis for exclusion if features of anxiety as described were also present, nor were hysterical conversion symptoms, provided these were accompanied by anxiety and did not dominate the picture.

TECHNIQUE

Our therapeutic technique was in no way different from that described by other workers. However, so that there shall be no question that our results are a consequence of faulty technique, this is now briefly described. We used the

Roche preparation of crystalline acetylcholine which was freshly prepared as a 10 per cent. solution in distilled water. This was given intravenously, a dose of 25 mg. being injected on the first occasion to test the sensitivity of the patient. Subsequently the dose was gradually increased to 200 mg. given in 2 c.c. The speed of injection varied with individual sensitivity and it was usual to inject 50 mg. rapidly, followed by the remainder more slowly in order to prolong the reaction. Occasionally the speed of injection could be considerably greater, and in some cases the whole of the 200 mg. could be given rapidly. The procedure with the controls, in respect of initial dose and gradual increase both of dose and speed of injection, faithfully imitated that with the patients receiving acetylcholine. The response of the patients receiving acetylcholine was as usually described. There was a sense of constriction in the chest, coughing, flushing, salivation, lachrymation and sweating. This was accompanied by a momentary slowing of the heart, and occasionally by cardiac arrest lasting for a few seconds. If cardiac arrest was of appreciable duration unconsciousness and convulsive movements ensued. Our aim throughout was to produce the milder reaction, accompanied by slowing of the heart, but to avoid the more severe consequences accompanying cardiac arrest. The speed of injection was varied to permit this result. Treatment was given twice weekly. Experience with our original series had suggested that genuine improvement, if it were going to occur, developed gradually between the limits of the sixth and fifteenth treatments and in no case did we get a satisfactory response in a patient who had not begun to improve by this latter stage. Occasionally patients showed a marked response after only one or two attendances, but this invariably proved to be spurious and was never sustained. No untoward incidents occurred in any cases treated by us.

RESULTS

Since they provide a standard of comparison with the results of other workers, as well as evidence of what may be expected of the treatment under the particular conditions existing in our clinic, figures have been given for 55 cases treated prior to the commencement of the control study.

In general the material is similar to that included in the later series, though a small number of obsessional neurotics, and tense homosexual psychopaths were also treated. For greater clarity remaining cases are classified into various groups. The first group consists of patients experiencing acute anxiety attacks, frequently of a phobic nature, precipitated by such situations as crowds, travelling or going out, but not unduly disturbed between attacks. The second group includes more chronically anxious patients whose anxiety was expressed almost exclusively in the psychic sphere, chiefly in the form of chronic tension. Many of these showed a strong obsessive component. Patients in the third group experienced anxiety predominantly in terms of awareness of its somatic concomitants, and should be distinguished from patients showing partial hysterical conversion. Patients showing anxiety complicated by a neurotic depressive admixture were placed in a fourth group and those in which some degree of hysterical conversion had occurred composed a final group. Four degrees of response were recognized, assessment being based on clinical impression, the patient's practical capacity, and his own account and that of a relative. Group I was either entirely symptom free or so very nearly so that the patients regarded themselves as having returned to their pre-illness state. Group II received definite but moderate benefit. Group III remained unchanged or showed such slight improvement as to be insignificant and Group IV became worse. The results are given in Table I.

Phillips and Hutchinson (1954) in their series used a somewhat different method of classification. They recognized three degrees of response, Improved, Unchanged, and Worse, and divided their material primarily according to the degree to which anxiety and tension were contained or alternatively projected through hysterical conversion mechanisms. Their first group was termed obsessive, in which phobic anxiety or tension, often running a phasic course, was the predominant feature, and would include the larger part of our first two groups as well as some of our third and fourth. Their second group consisted of patients where the picture was dominated by a single fixed symptom, for example a pain, and where also an obsessive component was postulated. A third group contained polysymptomatic anxiety hysterics with more prolific conversion symptoms. These latter two groups would both fall mainly into our fifth category. They also treated a number of obsessional neurotics, schizophrenics and psychopaths. Comparisons of the results of different workers are always difficult even when identical classifications are used, but we believe that our figures and those of Phillips and Hutchinson (1954) are not dissimilar.

In the control study, two groups of eighteen patients were treated. Comparisons of the two groups, according to a number of factors, namely age, sex, a history of previous neurotic traits, the presence of strikingly over-anxious or obsessive personality, intelligence, work record, the presence of a significant contemporary environmental or other problem, the duration and severity of the illness, and the number of treatments given, have been made in Table II. They are also compared diagnostically. It will be seen that there was no significant difference in the loading of any of these factors and that the two groups can in fact be accepted as comparable. Comparisons of response in the two groups are given in Table III. Not only are the results almost identical, but furthermore, responses in both treated and control group corresponded closely with those previously obtained in the larger uncontrolled series, and with the reports of other workers.

TABLE III
Results of Acetylcholine Therapy Controlled Trial

	Series	Total	Ac. Anx.	Chr. Ten.	Som. Anx.	Anx. Dep.	Anx. Hys.
I Symptom Free	Treated	6 33·3%	3	1	1	1	
	Control	8 44·5%	4	3	1		
II Improved	Treated	4 22·2%	1	3			
	Control	3 16·6%	2		1		
III No change	Treated	8 44·5%	1	1	1	2	3
	Control	6 33·3%			2	1	3
IV Worse	Treated						
	Control	1 5·6%					1
V Refused	Treated						
	Control						
Total	Treated	18	5	5	2	3	3
	Control	18	6	3	4	1	4

CONCLUSIONS AND COMMENT

Without doubt, attending for a course of acetylcholine therapy will produce favourable responses in a proportion of anxiety neurotics, and if treatment is restricted to the group of phobic anxiety and tension states or obsessive anxiety states, a high proportion of good results will be obtained. On the other hand it is clear that the curative property lies not in the drug administered but in some other aspect of the total therapeutic regime. The possible mechanisms involved are discussed elsewhere (Tibbetts and Hawkins, 1956) in the light, not only of these results, but also of a parallel study of carbon dioxide therapy. However, an important general conclusion may be drawn. Apparently convincing results obtained in the neuroses with a new treatment cannot be accepted as sufficient evidence of intrinsic merit in the allegedly active therapeutic agent, and a serious reappraisal may be required of some of the claims which have been made for a variety of procedures.

SUMMARY

(1) The literature reporting the use of acetylcholine in the treatment of psychiatric conditions is reviewed.

(2) The design of a controlled study, to test the efficacy of the recently introduced modified method for the treatment of neuroses is described.

(3) Results of treatment in 55 cases are reported.

(4) Evidence that two groups of 18 cases are comparable is presented.

(5) Results of the treatment of one of these groups with intravenous acetylcholine and the other with intravenous distilled water under identical conditions are reported.

(6) On the evidence that almost identical results were obtained in the two groups, and that results in the control group compare with those previously obtained by the authors and others when using acetylcholine, it is suggested that acetylcholine has no specific therapeutic effect in the treatment of neurosis.

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CARBON DIOXIDE INHALATION THERAPY IN NEUROSIS

A CONTROLLED CLINICAL TRIAL

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THE first recorded attempt to use carbon dioxide inhalation systematically as a form of psychiatric treatment was by Lovenhart *et al.* (1929). The subjects were catatonic schizophrenics and such modification as occurred was fleeting in nature.

In 1943 Meduna began to use carbon dioxide inhalation in the treatment of the neuroses and his efforts were described in a series of papers and developed in a monograph (1950). This contains a full description of the physiological and pharmacological effects of carbon dioxide upon nervous function and the technique of administration is described as are also the results in 100 patients. These results are taken as giving some support to a neurophysiological theory of the neuroses based on homeostatic and cybernetic considerations. Efforts were made to minimize the effects of "suggestion" and, although the difficulties are acknowledged, the following passage suggests that the author was reasonably satisfied with his precautions.

"To summarize, I exerted particular effort to avoid any possibility of heterosuggestion; and during the whole procedure I had no conscious vestige of it. Therefore, heterosuggestion as an integral part, or even as a factor of major importance, in the mechanism of improvements which I effected by the Carbon Dioxide treatment must be discarded.

"There are, however, two factors of suggestive character which I could not have excluded completely; the autosuggestion of the individual patients and the mass-suggestion generated by the patients in the waiting room."

The critical reader cannot fail to take note of the lengthy introspections which some patients submitted to the author and to question whether mechanisms may not have been set in motion other than those intrinsically or specifically related to carbon dioxide inhalation.

The publication of this work came at a time when, amongst one faction of psychiatrists, enthusiasm for physical measures of treatment was running high; the prestige of Meduna, resulting from his notable association with convulsive treatment, naturally gave particular stimulus to an interest in carbon dioxide inhalation treatment. As a result during the last five years the treatment has been used widely and the literature on the subject is extensive.

The authors have been conducting carbon dioxide therapy with out-patients for the past three years. Results obtained in a series of 79 patients are given below (Table I). It will be seen from the subsequent discussion that these were not greatly different from those obtained by other workers, though evaluation

TABLE I
Results of Carbon Dioxide Therapy

		Total	Psy. Anx.	Som. Anx.	Anx. Dep.	Anx. Hys.	Con. Hys.	Dep. Con.	Ob. Neur.
I	Symptom free	14 19.2%	8	3	2	1			
II	Improved	22 30.2%	7	2	1	6	5	1	
III	No change	34 46.5%	3		1	6	15	4	5
IV	Worse	3 4.1%	1					2	
V	Refused	6	3				3		
	Total	79	22	5	4	13	23	7	5

and comparison of results is made difficult by the use of varied techniques, the wide range of patients treated, the complicating factor of concurrent psychotherapy in some series and differing criteria for assessment. All this has prompted appeals for greater standardization from Jackman and Schorr (1952), Peck (1953), and Frank (1953). Frank, in particular, stresses the desirability of a control series using a different inhalant.

In the absence of any satisfactory control study comparing carbon dioxide with an undoubtedly inert substance, and having in mind considerations such as prompted our acetyl choline experiment, it was decided to conduct a similar controlled clinical trial.

DESIGN OF THE EXPERIMENT

As in the case of our acetyl choline trial we desired to arrange for two similar groups of patients to pass through an identical therapeutic regime except for the critical issue of receiving or not receiving carbon dioxide. The therapeutic setting, to which we attach considerable importance, has already been discussed in connection with the other trial (1956). Original case selection and subsequent assessment was at no time carried out by the psychiatrist directly concerned with the treatment and selected cases were divided randomly into treated and control groups without the relevant information being passed on to selector or therapist. When the patient attended for his first treatment, the only member of the clinic staff to know if he was to be a treated or control case was the sister in charge.

As an inert control substance it was decided to use compressed air. This was preferred to oxygen, to nitrous oxide and oxygen, or to oxygen spiked with carbon dioxide as suggested by Frank on account of its unquestionable therapeutic inactivity. Two identical cylinder trolleys were obtained and adjustable cloth covers were made which completely disguised the differently marked cylinders from both therapist and patient. Sister arranged for the porter to place the correct cylinder trolley in the appropriate cubicle, but otherwise remained entirely in the background as far as the carbon dioxide treatment was concerned; the operator was assisted by a staff nurse who was unaware that an inert substance might be given. As in the case of the acetyl choline trial, these precautions were designed to obviate any unconscious difference in presentation of the first critical treatment, since at that time the operator was unaware which

accompanied by certain sensations; if these did occur they would consist of breathlessness, deep panting breathing, dizziness and perhaps a momentary "blackout". It was emphasized that a satisfactory therapeutic response in no way depended on the occurrence or otherwise of these events, and could be anticipated as treatment progressed. This was also the explanation given to the staff nurse assistant.

At four weekly intervals patients were reviewed by the original selectors, who throughout remained unaware which patients were controls, and who avoided questions concerning immediate reactions, such as might provide a clue. A proforma similar to that reproduced in connection with the acetyl choline trial was used. It seemed to us that the two criticisms most likely to be levelled at our experimental procedure were those already discussed in connection with that study. Once again, however, a random division of an approximately homogeneous clinical group produced two series quite surprisingly similar in all essential particulars (see Table II); these, we suggest, go far to counter the criticism that our two groups may not have been comparable. Had there been significant discrepancy between results in treated and control groups, it might reasonably have been suggested that these were due to the differing subjective experiences of the patients. Since, however, such differences were not found, this criticism does not hold good.

SELECTION OF PATIENTS FOR THE TRIAL

Studies of the effects of carbon dioxide treatment have been greatly confused by variation in techniques, differing diagnostic criteria and the wide diversity of patients selected for treatment. Our aim in this experiment has been to attain a reasonable degree of homogeneity. With this in mind we have excluded those clinical conditions in which, in the light of preceding experience, response was improbable.

Although carbon dioxide has been tried in the treatment of the psychoses (Lorenz and Waters, 1929; Meduna, 1950; and Liest, 1952), claims are for the most part unenthusiastic or unconvincing. We have excluded absolutely all patients suffering from schizophrenia, psychotic depression of any type and the organic psychoses. Baudouin *et al.* (1947) reported favourable results in 8 of 10 epileptic patients. Meduna (1950) found no improvement in 4 patients suffering from psychomotor epilepsy. We have treated no epileptics in this way.

Although many of our patients had defective personalities, we did not include patients in which this was the primary consideration. We also excluded alcoholics and perverts. We found it difficult to believe that carbon dioxide treatment would be likely to bring about persistent improvement in psychopaths, although it is only fair to say that in Frank's interpretation of the results of other workers, there are two series in which reasonable numbers of personality disorders, alcoholics and perverts are included. These are Meduna's (1950) series in which 25 of 32 showed improvement and Kindwall's (1949) cases in which 11 out of 19 received apparent benefit.

By common consent obsessional compulsive neurotics do not improve with carbon dioxide treatment, although Jackman (1953) has made claims for intensive treatment using a special technique. There were five obsessionals in our original series and in the control series three patients are described as obsessional; they suffered from depersonalization and the obsessional basis for this became evident only during the course of treatment. Acute anxiety, with a tendency to panic was regarded as a partial contraindication because of the tendency for the treatment to aggravate acute anxiety. No stutterers were treated.

The remaining patients included those with anxiety states with various types of elaboration. These were partial or complete hysterical conversions, autonomic instability, phobic symptoms and psychosomatic disorders, such as colonic irritability, pruritus and asthma, but no rheumatoid arthritis (Locke and Cohen, 1940). These patients would fit into Meduna's three groups: sympathetic reactions, parasympathetic reactions and motor reactions; in the classification of the Diagnostic Manual of the American Psychiatric Association (1952) used by Frank, the two relevant groups are (a) psychoneurotic disorders, (b) psychophysiologic, autonomic and visceral disorders.

We have included depressed patients where the depression has been of the neurotic type and has not completely dominated the clinical picture. Seven patients in the original series and 7 in the therapeutic trial (4 treatment and 3 control) are described as suffering from depressive conversion, but there was an affective aura and depression was present, though without any of the classical features of a depressive psychosis. It is our usual practice, if possible, to avoid or at any rate delay E.C.T. in such conditions. In some of these patients the somatic symptoms lessened with carbon dioxide treatment and depression came much more to the fore. A change was then made to E.C.T., often with satisfactory results.

TECHNIQUE

We have avoided the variants which include the "single breath" technique (La Verne, 1953) using a high percentage of carbon dioxide, and the combined use of nitrous oxide (La Verne and Herman, 1953). We have also avoided techniques in which evaluation is complicated by psychotherapeutic considerations; these include a method devised by Milligan (1951) and calculated to favour abreaction and also the so-called "psychopenetration" described by Wilcox (1951) in which the essential features are in each treatment a graduated increase of carbon dioxide concentration to high levels and the concurrent use of psychotherapy.

To avoid confusion, our technique which closely follows the prototype devised by Meduna (1950) is outlined briefly. A mixture of 30 per cent. carbon dioxide and 70 per cent. oxygen was administered from a ready-mixed cylinder, through a mask with a large breathing bag connected through a reducing valve, which permitted a gas flow of 20 litres per minute or more. Sufficient was given to result in unconsciousness, which usually required from 20 to 30 breaths, though occasionally considerably more were necessary.

Unlike Meduna and a number of subsequent authors who sought to produce unconsciousness at the first visit, we accustomed our patients to the experience by commencing with as few as five breaths, only reaching an anaesthetic dose on the third or fourth treatment; we believe that this greatly contributed to the small number of cases in which treatment was broken off. In other respects our method was identical. The procedure with the controls, in respect of initial dose and subsequent increase, faithfully imitated that with the patients receiving carbon dioxide except, of course, that hyperpnoea and unconsciousness did not result.

The immediate response of the treated group was as described by Meduna, and we saw in various patients autonomic reactions such as flushing and sweating, muscular tremor, twitching, rigidity and spasms, and emotional reactions with weeping, screaming and violent outbursts; the pattern for each individual patient remained very similar throughout. Like most other workers we found that if genuine improvement were going to occur there was evidence to this

effect between the outside limits of the eighth and seventeenth treatments; in no case did we get a satisfactory response where there was no sign of improvement by this latter stage. Though in our original series we persisted much longer, in our control experiment we followed Meduna's advice and discontinued treatment if no improvement had occurred after 20 to 25 treatments.

As in our acetylcholine trial (1956) and as also noted by Meduna (1950), occasionally "pseudo-improvement" occurred after only one or two attendances to be followed almost immediately by relapse to the pre-treatment level. In no case was this early response sustained.

No untoward incidents occurred in any cases treated by us.

RESULTS

In his 100 cases Meduna reported improvement in 68. The best results were found where visceral and autonomic disorders were prominent and the least good in stutterers and psychoneurotic disorders. Personality disorders occupied an intermediate place. Frank (1953), in his excellent review, has reclassified the results reported by 11 groups of workers in order to attain some degree of standardization. The total number of patients treated was 238 and the improvement rate was 61 per cent. Taking all the figures into account, the best results were found in "psychophysiologic disorders" and the worst in stutterers. Psychotics and pure obsessionals were not included.

More recently Clark has reported on results with 42 out-patients. He found an improvement rate of 48 per cent. but observed that if his 4 obsessional patients and the 16 who had less than 10 treatments, were excluded, the improvement rate rose to 73 per cent.

Our results are classified into a number of diagnostic sub-groups. Group A consists of patients suffering from anxiety expressed predominantly in the psychic sphere as acute panic or phobic attacks or more usually as chronic

TABLE III

Results of Carbon Dioxide Therapy Controlled Trial

	Series	Total	Psy. Anx.	Som. Anx.	Anx. Dep.	Anx. Hys.	Con. Hys.	Dep. Con.	Ob. Neur.
I Symptom free	Treated	5 20.8%	4	1					
	Control	5 20.8%	3	2					
II Improved	Treated	6 25%	2		1	2	1		
	Control	7 29.2%	3	1	1	1	1		
III No change	Treated	12 50%	1			2	5	3	1
	Control	12 50%				1	6	3	2
IV Worse	Treated	1 4.2%						1	
	Control								
V Refused	Treated	1					1		
	Control	1					1		
Total	Treated	25	7	1	1	4	7	4	1
	Control	25	6	3	1	2	8	3	2

tension. Group B were patients experiencing anxiety in the form of autonomic instability. Group C were patients in whom anxiety was complicated by neurotic depression. Hysterical patients fell into groups D and E. In the former, conversion was only partial and anxiety was still apparent whereas in the latter somatic conversion was more or less complete. Group F is formed by the patients described above as suffering from depressive conversion and Group G is constituted by the patients with obsessional states. In the controlled trial obsessionals were excluded except for the patients with depersonalization already referred to.

Four degrees of response were recognized. Group I was either entirely symptom-free or so very nearly that the patients regarded themselves as having returned to their pre-illness state. Group II received definite but moderate benefit. Group III remained unchanged or showed such slight improvement as to be insignificant and Group IV became worse. Group V are the patients who discontinued treatment.

In our original series of 79 cases almost exactly half of those completing treatment showed some improvement (Table I). In the controlled trial with 50 patients (25 control and 25 treated), a total of 23 showed improvement (Table III). Discarding the two patients not completing treatment, the improvement rate was 48 per cent., which was almost identical with that in the original series; of those who improved, 11 were treated and 12 were controls.

CONCLUSIONS AND COMMENTS

It seems clear that regular attendance at a hospital department will, under certain conditions, bring about improvement in a substantial proportion of neurotic patients. On the other hand there does not appear to be any distinction between those patients who attended in order to receive carbon dioxide treatment and those who attended for compressed air. The conclusion which we draw from this finding is that the improvement which has been demonstrated is the result of a regime rather than of any pharmacological action of carbon dioxide. The numbers in the sub-groups are too small to permit firm conclusions, but in this trial there is a suggestion that anxiety in its manifest forms reacts more satisfactorily than does hysterical conversion.

The over-all response with the carbon dioxide (50 per cent. and 48 per cent. improved) compares unfavourably with the acetyl choline results (60 per cent. and 50 per cent.). Some might conclude from this that carbon dioxide was inferior as a treatment. In fact we believe that the differences are accounted for by case selection, a higher proportion of less promising patients being selected for carbon dioxide treatment.

SUMMARY

(1) The literature discussing the use of Carbon Dioxide treatment for psychiatric conditions is reviewed.

(2) The design of a controlled study to test the efficacy of this method of treatment in the neuroses is described.

(3) Results of treatment in 79 cases are reported.

(4) Evidence that 2 groups of 25 cases are comparable, is presented.

(5) Results of the treatment of one of these groups with a Carbon Dioxide-Oxygen mixture and the other with compressed air under identical conditions are reported.

(6) On the evidence that almost identical results were obtained in the two groups and the results in the control group compare with those previously obtained by the authors and others, it is suggested that Carbon Dioxide has no specific therapeutic effect in the treatment of neurosis.

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THE PLACEBO RESPONSE

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IN recent controlled trials, conducted by the authors (1956), we were interested to note the proportion of patients improving with the administration of placebos. A placebo is defined in the *Shorter Oxford Dictionary* (1944) as "A medicine given more to please than to benefit the patient". It is presumed that, implicit in this definition, is the qualification that the doctor is aware of the relatively inert qualities of the substance, whilst the patient is not. There is, of course, a type of patient who derives considerable benefit mainly by virtue of the fact that he has been pleased. In spite of the discovery of increasing numbers of drugs with specific properties, the prescription of placebos is still common practice. Dunlop *et al.* (1952) analysed over 17,000 prescriptions of which about one-third were tonics, stomachics or sedatives; although barbiturates cannot strictly be called placebos, the spirit in which they are prescribed frequently puts them near to this category.

The definition in the *American Illustrated Medical Dictionary* (Dorland, 1951)—"An inactive substance or preparation, formerly given to please or gratify a patient, now also used in controlled studies to determine the efficacy of medicinal substances"—is more comprehensive and embraces modern usage. The usefulness of the placebo in controlled therapeutic trials is now generally acknowledged: this is nowhere more true than where psychiatric practice is concerned, because a substantial proportion of emotionally disturbed patients show favourable responses to any therapeutic effort which combines enthusiasm, impressiveness and benevolence. This apparent platitude is justified by a study of psychiatric publications, which will at any time demonstrate how frequently the principle involved is overlooked.

The work of Stewart Wolf and his collaborators (1950) has stimulated a more sophisticated and precise interest in the subject. They performed interesting experiments on the patient Tom, who had a gastric fistula. It was possible to demonstrate by direct observation that the effects of some drugs (Urogastrone, Benadryl, Pyribenzamine and Posterior Pituitary extract) on the gastric function were directly dependent on Tom's emotional state. For instance when Tom was relaxed, administration of Urogastrone caused cessation of gastric function but when Tom was already provoked the same substance increased gastric activity. An injection of sterile water enhanced gastric blood flow. In another experiment a patient suffering from nausea and vomiting of pregnancy (usually associated with flaccidity of the stomach) was given 10 c.c. of syrup of ipecacuanha and told that it would reduce her nausea. This it did and the stomach resumed activity within 20 minutes. The responses with prostigmine were comparable. Tom, too, was given prostigmine, which produced abdominal cramps and diarrhoea; when this was followed by the administration of lactose and tap water the same results were obtained. Wolf's conclusions were that the important factors are the state of the end-organ at the time of administration, the setting (i.e. the route, presence of experimenters, etc.), and conditioning circumstances.

In another paper Stewart Wolf and Pinsky (1954) report their observations on 31 out-patients who acted as their own controls. They were anxious, tense patients, some of whom had psychosomatic complications such as peptic ulcer and migraine. The results with mephenesin tablets and an inert placebo showed that in either case 20–30 per cent. were better, 50–70 per cent. unchanged and 10–20 per cent. worse. More surprising was the fact that minor side-reactions such as light-headedness, drowsiness and anorexia occurred frequently with both mephenesin and placebo and in three cases there were major reactions. Administration both of mephenesin and placebo was followed in one case by overwhelming palpitations, weakness and nausea, in another by a diffuse erythematous rash and in a third by epigastric pain, watery diarrhoea, urticaria and angioneurotic oedema. Other interesting examples of placebo responses are quoted by the authors.

The concept of the “placebo reactor” (Beecher *et al.*, 1953; Lasagna *et al.*, 1954) is a useful one and has carried enquiry a stage further. Lasagna and his collaborators studied 162 patients who had undergone surgical operations. They devised a method of studying the effects of morphine and of saline on post-operative pain. In this way they were able to differentiate between “placebo reactors” and “non-reactors”. The reactors were on the whole five years older but there was no sex differentiation. Reactors on the whole tended to be more expansive, co-operative and uncomplaining; they were more regular Church-goers, had less formal education, and their reactions to stress were more readily translated into somatic form.

In a controlled clinical trial comparing the effects of carbon dioxide treatment with inhalation of compressed air, the authors (1956) found that about 50 per cent. of patients improved irrespective of whether they had carbon dioxide or the inert substance. Similarly in a controlled trial (1956) comparing the effects of intravenous acetyl choline and sterile water, about 60 per cent. of the patients improved, again irrespective of whether the pharmacologically active or inert substance was administered. The slightly better results in the latter trial are probably explained by more discriminating case selection, as judged by premorbid personalities and the duration and phasic quality of the illness.

The patients used as controls received substances which are unquestionably inert and we regard those deriving benefit as placebo reactors. Since no difference could be shown between results in the treated and control series, it seems reasonable to believe that cases responding to “treatment” were also showing a placebo response.

In the combined control series there are 43 patients in all. One of these gave up treatment at an early stage and another was worse after treatment. Some of the features of the remaining 41 patients are analysed in the Table.

Estimation of improvement was based on clinical impression by the assessor (who was ignorant as to which patients were in the treatment or control series), on practical capacity and on the patient's own statements, usually amplified by independent statements of a friend or member of the family. Patients were divided into three groups. In Group I recovery was virtually complete; in Group II definite improvement was seen and in Group III there was no material change. We are not concerned at this stage with follow-up figures since immediate response is what is under consideration; no doubt the follow-up, which we intend to undertake, will show a significant number of relapses.

The numbers are small and justify impressions rather than firm conclusions. It would seem that youth, if anything, favours placebo response. Sex distribution

is similar but the presence of previous neurotic traits and hysterical or inadequate features in the personality militate against a positive placebo response.

TABLE I

The Placebo Reaction

		Factor			I	II	III
Total	..	..	..	..	13	10	18
Age	..	Minimum	..	..	22	28	28
		Average	..	..	32	38	42
		Maximum	..	..	42	59	55
Sex	..	Male	..	..	7	4	10
		Female	..	..	6	6	8
Neurotic traits	..	Childhood	..	..	3	1	6
		Adult	..	..	2	2	8
Personality noted as	..	Over anxious	..	..	6	4	4
		Obsessive	..	..	4	4	9
		Hysterical	..	..		2	8
		Inadequate	..	..			3
Intelligence	..	Below average	..	..		1	2
		Average	..	..	9	8	14
		Above average	..	..	3	1	3
Work record	..	Stable	..	..	13	10	15
		Unstable	..	..			3
Environmental problem	..	..	..	..	5	4	8
Duration of illness	..	Minimum	..	..	0.5	1.0	0.7
		Average	..	..	3.0	5.7	8.7
		Maximum	..	..	7.0	14.0	50.0
Pattern of illness	..	Phasic	..	..	7	4	4
		Non-phasic	..	..	6	6	14
Severity of illness	..	Moderate	..	..	10	9	14
		Severe	..	..	3	1	4
Diagnostic group	..	Psychic anxiety	..	..	10	5	
		Somatic anxiety	..	..	3	2	2
		Anxiety depression	..	..		1	1
		Anxiety hysteria	..	..		1	4
		Conversion hysteria	..	..		1	6
		Depressive conversion	..	..			3
		Obsessional neurosis	..	..			2

Nothing useful emerges from a consideration of intelligence and work record. We had expected that the presence of an obvious contemporary environmental problem would prejudice placebo reaction but this does not seem to be the case. As would be anticipated, a greater duration of illness prior to treatment and an unremitting pattern of illness both lead to smaller numbers of positive placebo responses. On the other hand severity seemed to have little effect on improvement.

The fallacies attendant on diagnostic sub-groups are fully appreciated and it is well known that independent clinicians will use different criteria, depending

on their experience and persuasion. The nature of the clinical sub-divisions used by us has been described in the reports of our acetyl choline and carbon dioxide therapeutic trials. Not only in the combined control series but in each of our groups of patients, totalling 220, whether treated by acetyl choline, carbon dioxide or inert substances, one trend stands out clearly and consistently. This trend is to the effect that patients with unelaborated anxiety are those most likely to respond in a positive manner to a placebo administered under the circumstances described. Somatic elaboration with a physiological basis does not greatly prejudice this response, but hysterical conversion affects it adversely. The fuller the conversion, the more resistant is the patient. The three patients in the controlled series, in which hypochondriacal symptoms proved to be based on depression, were non-reactors, as were also two obsessional neurotics.

It would seem to us inescapable that the placebo reaction must be a manifestation of suggestion, using this term in its broadest sense. If indeed this is so, our findings concerning its relation to hysterical conversion are at variance with popular belief. The notion of a special relationship between hysteria and suggestibility originated in France during the last century and though hysteria had then a somewhat different meaning from its contemporary one, this idea has had universal influence up to the present day. Such a relationship is certainly assumed by many workers in assessing the results of new treatments, so that greater efficiency in non-hysterics is regarded as evidence that the substances do not act by suggestion. Such has been true of the two methods under review at present, namely carbon dioxide inhalation therapy and acetyl choline therapy. Concerning the former Meduna (1950) says—"of the whole group of patients my treatment of whom I am reporting, hardly 3 per cent. were conversion hysterics, the par excellence suggestible group", while Sargant (1952), writing of acetyl choline therapy, would seem to have much the same in mind when he says "we have not so far found that it helps the hysterical patient more than any other new treatment with a highly suggestive value".

Approaching the problem of suggestibility from the standpoint of tests claimed to measure this trait, psychologists were able to produce little evidence of any correlation with hysteria. The relevant literature has been well reviewed by Eysenck (1947) who also reports on extensive experimental work conducted with various colleagues. He describes two quite uncorrelated and independent factors operating in the tests customarily used; primary suggestibility which concerns the suggestion of movements, and secondary suggestibility which concerns the suggestion of sensations or perceptions. Prestige suggestibility, he thought, might perhaps be a third factor. He showed primary suggestibility to be related both to ability to be hypnotized and to "neuroticism" as this is understood by him, but to be in no way positively related to hysteria. In fact, dysthymics were if anything more suggestible than hysterics, with suggestibility in hysteria tending, as Bleuler (1924) has suggested, to operate in a negative direction. It is difficult to see in what relationship this somewhat abstracted type of suggestibility stands to the reactions so far described in this paper or to suggestion as it is generally met with in the clinical sphere. Certainly, however, Eysenck's findings are more in keeping with our own than with the popular view.

To explain his data Eysenck invokes the concepts of aptitude and attitude. In the case of primary suggestibility aptitude is a tendency for the thought of a movement to be accompanied by an incipient movement of the muscles involved. In practice this aptitude is influenced by attitude, the desire of the

subject to resist or not to resist the suggestion. Of the two it would seem to us that attitude is likely to have greater clinical significance. In this respect there is undoubtedly a striking difference between the test and clinical situations. Whilst in tests the suggested material is essentially neutral in type and attitude may be determined mainly by instructions given, clinically patients are being asked to modify meaningful symptom patterns.

If neurotic illness is viewed from this standpoint it would seem possible that a positive attitude towards symptomatic improvement may more usually be associated with dysthymic than with hysterical illness, since in the latter powerful motives of secondary gain militate against progress. Other things being equal, it is then perhaps reasonable to expect that therapeutic suggestion might prove more effective in the dysthymic group, and our own results with the mild implied suggestion of inert placebos do indeed indicate that this may be so.

What then of the customary view of the association of hysteria and suggestibility, which must surely refer to some observable phenomenon? We believe our confirmatory finding of what Meduna (1950) termed "pseudo-improvement" is of significance here. This consists of dramatic symptomatic relief in the very early phases of treatment followed a little later by relapse. By contrast with the more gradual sustained response, this occurred almost exclusively in hysterical patients and is of course much more reminiscent of what frequently happens after treatment by hypnotic suggestion. Being a striking phenomenon it might well account for the conventional view. This also could be principally a matter of attitude. What for the dysthymic might appear to imply a showy, shallow, and superficial process, could seem dramatic and exciting to the hysteric. As treatment progresses, more fundamental attitudes, perhaps as we believe influenced by subtle modifications of family attitude, are likely to prove of greater importance.

We have not, as yet, made a systematic study of domestic influences, but hope to do so later. The sort of mechanisms we have in mind may, perhaps, be made clearer by an example. A woman may develop an anxiety state with headache and vasomotor disturbance. She has real symptoms, but is told by her general practitioner and by a physician at the hospital that her trouble is "all due to nerves". The husband, either from impatience or because he believes it to be in his wife's interests, adopts a stern and coercive attitude. This is interpreted by the patient as due to lack of sympathy and may lead to symptoms of a more florid kind. If then, the patient is referred to a psychiatric out-patient clinic and treatment is "by talking", the husband will regard this as confirmation of his view that the symptoms are "imaginary". If on the other hand the patient is directed to attend regularly for injections or inhalations involving unconsciousness, the implication is that real suffering is involved. Family attitudes change; the patient's self-esteem is bolstered by facing and surviving repeated physical ordeals and morale is stimulated by the camaraderie of a clinic where others are doing the same. The scene is set for improvement. We believe that we have observed processes of this kind many times.

Administrative, economic and academic reasons should prompt us to establish so far as possible how the results of treatment with a placebo contrast with those following psychotherapy and to what extent they are enhanced by psychotherapy. This cannot be an easy task because there are so many variables contained in the term psychotherapy. These include intensity and circumstances of treatment, personality of the therapist and even possibly the dogma to which he subscribes: and psychotherapy, using the term in its broad rather than its restricted sense, is bound to be implicit in regular clinic attendance however

far deliberate suggestion, abreaction and explanation are avoided. We believe that Meduna and many others have underestimated the importance of the psychological changes brought about by such attendance.

The findings of Harris (1954) are interesting in this connection. In the Out-patient Department of the Maudsley Hospital 120 psychoneurotic patients were divided into two groups, allocation depending on the spin of a coin. One group was treated by psychotherapy, the other by carbon dioxide inhalation, following the Meduna technique. On assessment a year later no significant difference between the two groups was found. Frank (1953), in his interpretation of 238 cases, found no significant differences in the results where psychotherapy was undertaken in association with carbon dioxide treatment as compared with those series of cases in which it was not. The findings of Atoynatan *et al.* (1954) are slightly at variance with those of Frank. They treated 48 anxious patients, 26 receiving nitrous oxide inhalations followed by carbon dioxide, whilst 22 patients received nitrous oxide alone. The difference in improvement was not statistically significant. The patients were grouped further into the "permissive" in whom discussion with a therapist was allowed and a "non-permissive" group in which it was not. In the permissive group the greater improvement as compared with the non-permissive group was of statistical significance. The authors' conclusion that the therapeutic setting contributes more to improvement than the gas involved is in line with our beliefs. One would certainly expect from general experience that opportunity to discuss the treatment and its effect on symptoms would favour improvement; but "permissiveness" is not the same thing as formal psychotherapy.

This paper has not been presented in any spirit of iconoclasm. What we have attempted to do is to indicate that, in our opinion, a more critical attitude is needed towards novel physical treatments. Some of these will prove, in time, to have almost specific properties and we believe that E.C.T. comes in this category; others, of which insulin coma treatment may be an example, have intrinsic but not specific value. The majority are likely to prove to be placebos, producing temporary improvement in something like 40-70 per cent. of patients. Even so it may be that they have their place. If future findings do justify the enlightened use of the more elaborate placebo, one difficulty is anticipated; it is hard for a team to maintain its enthusiasm about the use of an inert substance unless that enthusiasm is fired and maintained by a specific objective, such as a research project; and it may well be that enthusiasm is one of the more effective ingredients of the therapeutic situation.

Certainly recognition of the mode of action of a treatment is vital for real advance. Without this knowledge unnecessarily complex and even hazardous treatments may continue to be used and the results of treatment may mislead physiologists and pharmacologists in developing their theories. Similar observations could well apply to formal psychotherapy. It still has to be shown that psychoanalysis has specific advantages and, for instance, that patients treated by Freudian methods do better than those submitting themselves to Jungian analysis or, indeed, better than those treated intensively, enthusiastically and sensibly by a heretic.

Whether or not the placebo has a place in psychiatric treatment, it is certain that its use in an uncritical manner cannot be justified. Used in that spirit, it could make for laxity of diagnosis, a static approach to treatment and general stultification of effort. Perhaps the same can be said for psychotherapy.

SUMMARY

- (1) Reference is made to some of the literature relating to placebo response and to suggestibility.
- (2) The authors' findings with controlled groups receiving intravenous acetyl choline, carbon dioxide inhalation and inert substances are considered in relation to placebo response.
- (3) Differential factors favouring placebo reaction are discussed.
- (4) A more critical attitude, both to the use of physical methods and of psychotherapy, is advocated.

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CEREBELLAR AGENESIS

By

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DEVELOPMENTAL defects of the cerebellum may take various forms: agenesis of the entire cerebellum; aplasia of one or both hemispheres, or aplasia limited to the vermis. It is the purpose of this communication to review the first two groups and to place on record the clinical and pathological features of a case in which but for one small fragment the cerebellum was wholly absent.

COMPLETE ABSENCE OF THE CEREBELLUM

The earliest recorded case, reported by Combettes (1831), was that of a low-grade epileptic imbecile, Alexandrine Labrosse, who died at the age of eleven. She did not speak until her third year and her articulation was always very defective. She had weakness of the lower limbs and did not learn to walk until she was five years old. Often she fell. She used her hands freely and could feed herself. For the last four years of her life she was confined to bed and usually lay with her head inclined to the left. At the post-mortem examination it was noted that the meninges were normal, the tentorium cerebelli was present and the cerebral hemispheres a little larger than normal. In the space normally occupied by the cerebellum there was a gelatinous membrane connected to the medulla by membranous pedicles. In their neighbourhood there were two detached pea-like masses of white matter. The quadrigeminal bodies were intact and at a lower level the aqueduct of Sylvius could be identified in the midst of tissues which seemed to have undergone some form of softening. In the medulla this softening had to some extent encroached on the restiform and olivary bodies. There was no fourth ventricle, no pons Varolii and the pyramids diverged to enter directly the crura cerebri. Flechsig (1883) also reported a total defect in a new-born child but the details of the case are too fragmentary to have any value.

A third example of total absence of the cerebellum has been described by Priestley (1920). Her patient was a spastic hydrocephalic infant of four months. There was no vestige of cerebellum, peduncles or pons. "On exposing the brain it was found to be extremely distended; the brain matter formed a thin layer over the ventricles which contained about $1\frac{1}{2}$ pints of clear fluid. The fourth ventricle was covered by a thin sheet (0.5 mm.) of tissue running from the corpora quadrigemina to the dorsal surface of the medulla. On the ventral surface the pyramidal tracts appeared to run up to the corpora quadrigemina. The base of the skull showed three pairs of fossae but there was no tentorium cerebelli. The lower end of the vertebral column was ill-developed; the arches of the fourth and fifth lumbar vertebrae were absent, as, too, were all the sacral segments."

PARTIAL AGENESIS

In cases of partial agenesis of the cerebellar lobes and vermis the extent of the developmental failure varies widely and of the numerous reports which have appeared the following are the most noteworthy.

In a rachitic cretin of 19 years who during life had difficulty in walking and speaking, Verdelli (1874) found a minute cerebellum measuring not more than 2 cm. in its transverse diameter. Leyden (1876) reported two cases of

almost total agenesis. In the first the cerebellum was reduced to the size of a bean and in the second it was represented by two minute masses, possibly "rests" of the flocculi. Other developmental anomalies present in both cases were hydromyelia, syringomyelia and meningocele. In the case described by Borrell (1884) the left cerebellar hemisphere was the size of a haricot bean and the right only slightly larger.

Ferrier (1886) described the brain of a female imbecile, aged 15, who was said to have walked well and steadily, though she was never known to have run. The cerebellum was of a most rudimentary character. The left lobe which constituted the main portion, possessed a superficial area of not more than one half inch square. In an imbecile woman aged 48, Fusari (1891) found almost total absence of the cerebellum. The failure of development involved the lateral lobes, the vermis and the flocculus.

The case recorded by Warrington and Montserrat (1902) was that of a female infant, aged six weeks, who presented a lumbar spina bifida, hydrocephalus and paraplegia. The cerebellum showed a very marked degree of arrested development; in many places it was unconvoluted and represented by an undifferentiated mass of embryonic tissue and small cells. In a few areas of the lateral hemispheres there was a cortex in which the three strata of molecular, granular and Purkinje cells could be recognized. There was no trace of central gray nuclei, no olives and no arcuate fibres; the cerebellar peduncles were practically absent. The spinal cord showed a general attenuation and the presence of hydromyelia and syringomyelia.

Sternberg (1912) described the accidental discovery at autopsy of what at first sight appeared to be total absence of the cerebellum. His patient was a woman who succumbed to carcinoma of the stomach in her 46th year. On removal of the brain the tentorium cerebelli was seen to be represented by a slender crescent which lay above a shallow posterior cranial fossa. Removal of the meninges revealed on each side strands of white matter bearing on their surface a number of parallel fissures resembling those normally seen on the surface of the cerebellum. From their position the author inferred that they represented the flocculus. The quadrigeminal bodies were small and a rudimentary pons blended with the medulla, conspicuous for the large size of the pyramids. The olivary bodies appeared to be absent. The cranial nerves and vessels at the base were completely normal. Of the five cases reported by Vogt and Astwazaturow (1912) the first was found to have only traces of the cortex of the hemispheres and vermis. The olivary and red nuclei were normal.

Anton and Zingerle (1914) reported the case of a child, aged six and a half years, in whom there were severe disturbances of the motor system; ataxia, adiadochokinesis, difficulties in swallowing and speaking, convergent strabismus and horizontal nystagmus. Movements of the hands were freer in the recumbent posture than when the child sat up. The cerebellum was almost completely absent but two fragments of the flocculus were found, each possessing a well differentiated cortex in which Purkinje cells were present. In the distended fourth ventricle islets of tissue containing granule and molecular layer cells were present. There were no olives and the restiform bodies were rudimentary. Baker and Graves (1931) described the brain of a low grade imbecile, aged 19, who learnt to speak a few words and who could walk if helped. The cerebellum was reduced to proportions approaching complete absence; its stage of development corresponded to that normally reached in the middle of the third month of foetal life. A normal tentorium cerebelli separated the cerebral hemispheres from an almost empty posterior fossa below. Folia present on the surfaces of

the attenuated lateral lobes indicated that cortical differentiation had taken place. The medulla showed absence of the olives and an extremely wide rhomboid fossa. There was no evidence of hydrocephalus. In the case of Rubinstein and Freeman (1940) in spite of extreme attenuation in cerebellar development, ante-mortem signs did not develop until two years before the death of the patient at the age of 71 years. Detailed studies of the brain disclosed two fairly developed flocculi, a trace of vermis and three simple folia of the right lateral lobe.

In the two instances of cerebellar aphasia recorded by Lichtenstein (1943) the condition was to a large extent unilateral and is therefore of lesser interest.

The case now reported was at first considered to be an example of total absence of the cerebellum for it was not until naked-eye examination of the brain stem had been supplemented by careful examination with a hand lens that a single minute fragment of cerebellar substance was discovered. It lay beneath thickened pia-arachnoid closely applied to the right side of the pons and the piece of tissue had a superficial area of approximately 10 mm. and a thickness of 1 mm. Microscopic examination showed that it possessed the molecular, nuclear and Purkinje cell layers which characterize the cerebellar cortex. Though in this way deprived of the interest which attaches to complete agenesis, the developmental defect was of a degree more marked than in any of the examples referred to above and seems therefore to merit a full description.

CASE REPORT

The patient, Samuel W., was born in 1883. Delivery was difficult owing to the large size of his head and was associated with asphyxia. His appearance at birth was evidently abnormal as the doctor is said to have remarked that it would be better if the baby were to die. It is not known at what age he started to crawl but he did not learn to walk until his seventh year. Speech was acquired late and his articulation, although it improved as he got older, never became distinct. All movements were clumsily performed and according to his sister "his fingers were all thumbs". He was very slow in buttoning and unbuttoning his clothes and often he required assistance. In adolescence he learnt to smoke and was able to fill a pipe and to hold a cigarette. He stood balanced on his heels with his legs far apart and when seated hunched himself up on the edge of his chair. He had frequent falls but was able to climb stairs unaided. In bed he lay curled up and had a habit of rolling his head. He played with toys and was friendly with other children. In spite of his obvious mental defect he remained at an ordinary elementary school until the age of fourteen. Apparently he learnt nothing and when he left school could neither read nor write. He was kept at home where he looked after the feeding of hens and goats. He went out by himself and was well known in the village, finding amusement in watching things and in talking to people. He had a ravenous appetite and ate everything placed in front of him. For 39 years he was looked after by his mother, and on her death he was sent to a public assistance institution where he remained for nearly ten years.

In temperament he was good natured and easily managed. Though sexually mature he took no interest in the opposite sex. He had no knowledge of time and often stayed out until he was fetched home. He had, however, a good memory for faces and could recall people he had known long after his admission to hospital.

The family history contained little of importance. The patient was the fourth and only abnormal child in a family of seven. The father, a canal wharf man died of heart disease, aged 60. His mother died from the effects of a stroke at the age of 64. A maternal aunt had a mentally defective child with a large head and defective gait.

In 1932 Samuel was certified and sent to the mental hospital at Hatton, Warwick. He was then in his 49th year. On admission, he was observed to be a small, thin man with a high forehead (Fig. 1). He walked on a broad base, bending his knees very little and with his arms held away from his sides at an angle of about 30 degrees to the vertical. He could stoop to pick up a ball and could throw it quite easily. He dressed himself and managed his food quite well. His habits were clean. When he spoke he had a habit of developing a convergent strabismus. His articulation was indistinct, monotonous, rather staccato and slightly nasal. Vision was good and he could recognize people from a long distance. Mentally, he was an imbecile. He recognized coins and knew the names of the staff and of other patients with whom he associated. With great difficulty he could write his own name. He had a good memory. When excited by other patients he became spiteful and struck out. In 1934 he was reported to be occasionally noisy and abusive and to chatter unintelligible rubbish. From this time onward he showed an increasing tendency to fall but it was only a serious handicap during the last

twelve months of life. A year before death pallor of both discs was observed with a normal right pupil; the left showed no reaction to light or accommodation. There was hypotonia of all limbs. The plantar reflexes were normal; the tendon reflexes exaggerated. The Wassermann reaction was negative in both blood and cerebrospinal fluid. In April, 1938 the patient became confined to bed. He went downhill rapidly and on 5 May succumbed to lobar pneumonia. He was 55 years old.



FIG. 1.—The patient S.W. There is an obvious degree of hydrocephalus and the widely separated fingers of the left hand suggest the presence of dysmetria.

POST-MORTEM EXAMINATION

The necropsy was performed approximately 24 hours after death. Apart from the appearance usual in lobar pneumonia the pathological findings were limited to the central nervous system.

EXAMINATION OF THE BRAIN

As it was proposed to preserve the brain as a museum specimen, it was immersed in Kaiserling's solution, but after three weeks in this medium it was transferred to a solution of formalin. Large, and obviously hydrocephalic, the cerebrum had undergone some degree of distortion in the fixing medium. It had also been damaged, particularly at the base where there was an almost complete tear through the pons. Furthermore, in the process of fixation the brain stem had acquired an acute anterior flexion at the junction of medulla and pons so that the floor of the fourth ventricle was exposed to view. These artefacts together with the preliminary fixation in Kaiserling's solution made the subsequent task of microscopic examination one of considerable difficulty.

CEREBRUM

The lepto-meninges and vessels on the superior surface of the brain were normal. The two hemispheres were slightly asymmetrical; the right was a little smaller than the left and its parietal and occipital lobes were on a plane inferior to those of the other side (Fig. 2). The convolutions were large, simple and slightly flattened, there being a moderate degree of internal hydrocephalus. At

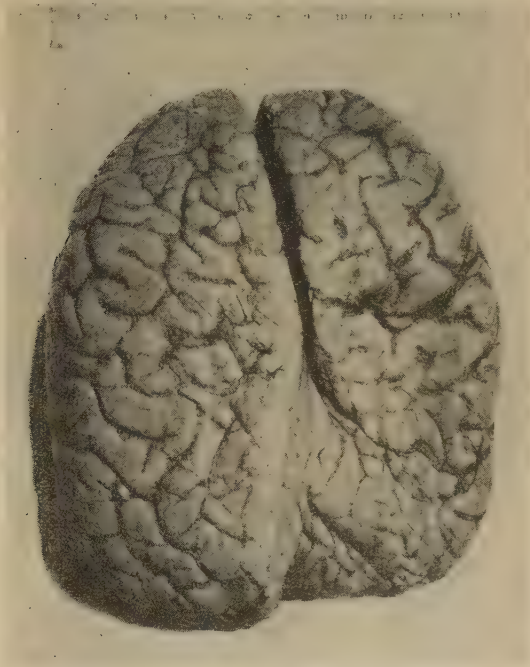


FIG. 2.—The cerebrum viewed from above, showing asymmetry of the two cerebra hemispheres.

the base, lying within the temporal and occipital lobes there was a large, roughly circular depression, covered by a conspicuous loose fold of pia-arachnoid which extended towards its anterior boundary. The cerebellum appeared to be entirely absent.

Proceeding from below upwards, it was possible to identify: a fragment of the cut cervical cord, remarkably normal in appearance; a flattened and attenuated medulla with, however, large and conspicuous pyramids; the bilateral absence of the inferior olives and the wide, flattened rhomboid fossa; the pons, very narrow in its width, bent caudally at the site of a transverse tear and joined to the midbrain by a continuation of the pyramids. The pons showed very little elevation on its ventral surface with no sharp demarcation between it and the cerebral peduncles, while the midbrain possessed a considerably dilated aqueduct, a relatively large tegmental area and a poorly developed basis pedunculi (Figs. 3 and 4). The corpora quadrigemina appeared normal and the roots of all the cranial nerves could be identified. On the ventral surface of the medulla the two vertebral arteries were prominent as they converged to form the basilar artery. On the right side of the brain stem at approximately the junction of the medulla and pons there was a loose membranous fold of tissue which when dissected off revealed the presence of a minute fragment of cerebellar

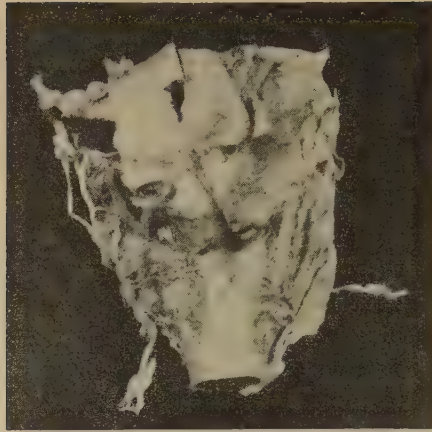


FIG. 3.—Ventral aspect of the brain stem. Note the relative smallness of medulla oblongata and pons. The midbrain shows a dilated aqueduct.

tissue. Inspection of the wide and shallow floor of the fourth ventricle showed that the striae acusticae were entirely absent. The roof of the cavity was represented by a partially detached thin membranous sheet, possibly of pia mater. The choroid plexuses were apparently absent.



FIG. 4.—Dorsal aspect of the brain stem. Note absence of the striae acusticae on the floor of the fourth ventricle.

MICROSCOPIC EXAMINATION

Frozen and paraffin sections were made of the cervical cord, the medulla at three different levels, the pons, midbrain, the vestigial fragment of cerebellum and the motor cortex.

The medulla oblongata was much smaller than normal and the enveloping pia-arachnoid showed a considerable degree of thickening. Sections through the lower third stained by the method of Loyez had a contour unlike that seen in normal preparations. The transverse diameter greatly exceeded the antero-posterior measurement and consequently the rhomboid fossa was extremely shallow and devoid of lateral recesses. The two pyramids were disproportionately

large and the olivary eminences entirely lacking. The dark staining fibres of the medial lemniscus were sharply defined and on the dorso-lateral aspects the wedge-shaped strands of cuneate and gracile nuclei were equally conspicuous. From their neighbourhood rather coarse bundles of internal arcuate fibres could be seen sweeping forwards to gain the medial lemniscus (Fig. 5). Closely applied



FIG. 5.—Section through the lower third of the medulla oblongata. $\times 3\frac{1}{2}$. The pyramids are relatively large and the internal arcuate fibres conspicuous. Arrow indicates the situation of olivary cells.

to the dorsal surfaces of the pyramidal tracts and separating them from the feebly represented formatio reticularis were two small areas of grey matter which in a rostral direction increased in size until they assumed the unmistakable appearance of olivary tissue.

In its middle third the medulla presented an even more abnormal appearance, its width being almost three times as great as its antero-posterior depth. As before the pyramids were prominent but they now presented on their dorso-lateral aspects two slightly convoluted bands of grey matter containing in very reduced numbers pigmented nerve cells characteristic of the inferior olive. To a considerable extent this part of the medulla owed its increased width to the presence on each lateral margin of closely aggregated bundles of nerve fibres which, if the cerebellum had been present, could legitimately have been regarded as entering into the formation of the restiform bodies (Fig. 6). Dorsal to these

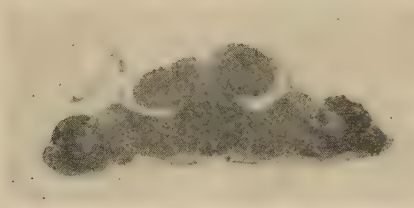


FIG. 6.—Section through middle third of medulla. $\times 2\frac{1}{2}$. Loyez stain. Note the presence of two curved bands of olivary tissue.

fibre masses and lying almost on the floor of the fourth ventricle were two discrete oval bundles, obviously those of the fasciculus solitarius. Two symmetrically placed areas of pallor immediately latero-dorsal to the olivary grey matter suggested maldevelopment of the spino-cerebellar tracts.

In sections through the upper third the medulla maintained its flattened shape and the two bands of olivary tissue had become reduced in size and less curved in outline (Fig. 7). The two lateral areas of pallor noted above were more pronounced. No fibres could be found in the situation normally occupied by the olivo-cerebellar tracts.

Pons. This part of the brainstem was considerably smaller than normal and its partial destruction from tears together with its preliminary fixation in an unsuitable medium had rendered it almost useless for histological study. None-



FIG. 7.—Section through upper third of medulla. $\times 2\frac{1}{2}$. Loyez stain.

theless, in the fresh unstained tissue it was possible to note that of its two divisions the tegmental was considerably larger than the pars basilaris. In the latter the compact bundles of the pyramids were criss-crossed by very few transverse fibres. Stains such as those of Weigert-Pal and Loyez failed to give satisfactory results with sections of the pons but they did, however, succeed in bringing into sharp relief the small fragment of cerebellar tissue, attached by a pedicle on the right side of the pons at the junction of the tegmental part with the floor of the fourth ventricle (Fig. 8). It measured no more than 7 mm. $\times$

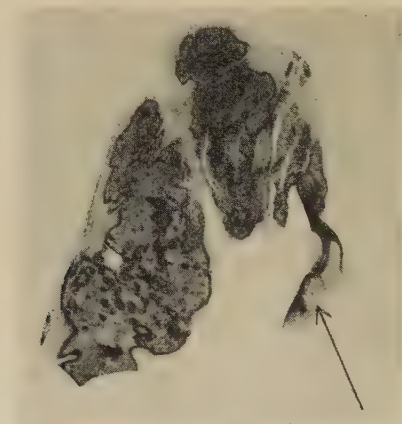


FIG. 8.—Section through pons. $\times 2\frac{1}{2}$. Loyez stain. The abnormal appearance is due to tears and the failure of the tissue to stain. Arrow indicates the situation of the cerebellar fragment.

3 mm. $\times$ 1 mm. A prolonged search on the opposite side failed to reveal any similar tissue. Thionin stained sections showed that it possessed the normal structure of cerebellar cortex and white matter though the Purkinje cells showed some irregularity of alignment and here and there gaps in their linear arrangement (Fig. 9).

Midbrain. The fibre bundles constituting the crusta, mesial fillet and posterior longitudinal bundle presented a normal appearance but those of the superior cerebellar peduncle were few. The heavily pigmented cells of the substantia nigra and the cells of the red nuclei appeared to be present in their normal numbers.

Motor Cortex. In this area the moderate degree of internal hydrocephalus had caused no disturbance of the normal arrangement of cell columns, though

possibly the Betz cells were less numerous than normal. Degenerate forms were present.

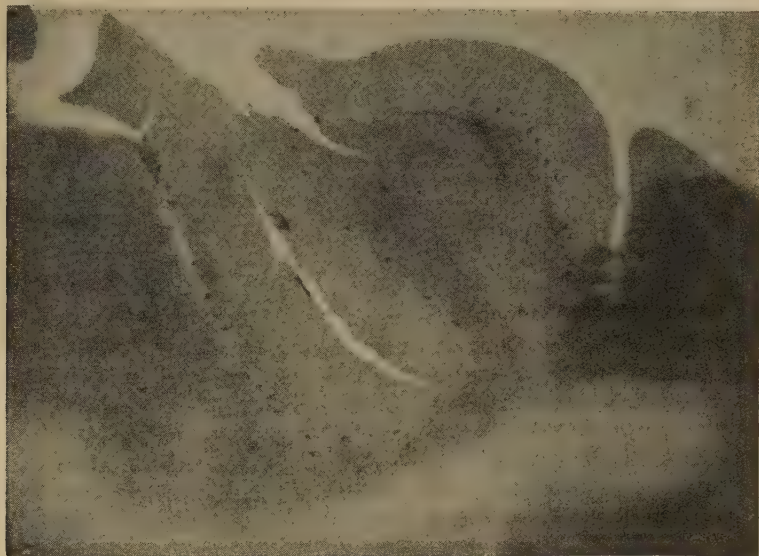


FIG. 9.—Fragment of cerebellar tissue. Cresyl violet stain, showing the almost normal differentiation into molecular, Purkinje and granular cell layers.

DISCUSSION

In an adult, the post-mortem discovery of a small cerebellum at once raises the question of whether it represents a failure of normal embryonic tissues to develop or a degenerative process of an atrophic or sclerotic character. When this doubt arises, a history of frank cerebellar signs is in favour of one or other of the many types of cerebellar disease for it is a remarkable feature of partial agenesis that it is not infrequently found in patients who during life exhibited no striking evidence of their serious structural anomaly.

In the case under consideration, though it was obvious that the patient was severely handicapped by disorders of voluntary movement which, as he grew older, became progressively worse, it seems clear from the post-mortem findings that his signs of cerebellar defect were the manifestations, not of an atrophic process, but of a true agenesis and of an extent so pronounced as to place the case almost in the category of complete aplasia. No loss of material, however severe, could be expected to reach the degree established in this case, for, as has been said, all that remained of the cerebellum was a single fragment of cortex and white matter, which on microscopic examination revealed the normal differentiation into molecular, granular and Purkinje cell layers. Moreover, the appearances in the brain stem and notably the conformation of the inferior olives were totally unlike those seen in a secondarily induced neuronal degeneration.

It is apparent that in the majority of cases of cerebellar agenesis the nervous system is affected at an early stage of its development and it will not have escaped notice that in the cases referred to above, in the more extreme degrees of agenesis it is almost invariably the pars floccularis which survives. Phylogenetically, the two flocculi are the primitive derivatives of the roof-plates of the metencephalon. They constitute the oldest part of the cerebellum and in human

development are among the earliest to make their appearance—probably not later than the second month of intra-uterine life. From this it may be inferred that the majority of cases of cerebellar agenesis occur after this period. In this case the position of the cerebellar fragment is not inconsistent with the view that it may have represented an imperfectly developed flocculus and its apparent limitation to the right side of the brain stem could easily have been due to the accidental removal of its opposite number on the left side of the pons. Small fragments of cerebellar tissue are readily overlooked and consequently, when based solely on unaided naked eye inspection, the claim for total absence of the cerebellum must remain open to doubt. In the case described by Combettes in 1831 his description of the presence of two small pea-like masses in the neighbourhood of the medulla resembles so closely that of Anton and Zingerle who were able to demonstrate the cerebellar structure of two nodules in a similar situation that it is difficult to avoid the conclusion that Combettes was describing a case which was not of total, but of partial, agenesis. Nor is the case recorded by Priestley wholly satisfactory since her claim for complete cerebellar deficiency rested on post-mortem appearances which were not supplemented by microscopic examination.

Normally, the development of the inferior olive affords an example of the embryological phenomenon of neurobiotaxis—the tendency of functionally related areas to establish connections—but from the findings in this case it is clear that a certain degree of independence is possible in the development of parts of the brain which are in closest connection with one another. Thus, though both palaeocerebellum and neocerebellum had all but failed to develop, the cells of the inferior olive which normally supply impulses to the cerebellum had survived to a considerable degree and showed no evidence of retrograde degeneration.

Foremost among the clinical features which deserve notice was the comparative freedom of movement in the upper limbs. Whereas in his station and gait the patient exhibited to a disabling degree the irregularities of movement which characterize cerebellar ataxia, except for the finer movements of the fingers, he was able to employ the upper limbs comparatively well. This has been noted in other cases of cerebellar agenesis in which both lateral lobes have been wholly wanting and is of interest inasmuch as the neocerebellum has developed through the ages as man became emancipated from the locomotive movements of the quadruped and learnt to use his fore limbs for more delicate purposive movements. It is therefore a paradox that deprived of his cerebellum the human subject should retain more command of his upper limbs than of his lower.

Attempts have been made to explain the absence of symptoms in cerebellar agenesis on the basis of compensations in neural structure. Anton and Zingerle (1914) concluded that compensation for the cerebellar defect is achieved by an hypertrophy of the dorsal sensory system, the spinal trigeminal and spinothalamic tracts on the afferent side, with hypertrophy of the pyramids and substantia nigra on the efferent side. It is, however, difficult to reconcile this view with the anatomical findings in the case described by Rubinstein and Freeman (1940). The cerebral peduncles were smaller than normal and in a much earlier study, Spiller (1896) made the same observation. In the case recorded above largeness of the pyramids was certainly a striking feature but microscopic examination of the motor cortex gave no indication of a compensatory hypertrophic development, nor were the cells of the substantia nigra more numerous than normal; if anything they were fewer in number.

More, perhaps, can be said for the alternative view that compensation can be achieved not so much through hypertrophy of extracerebellar tracts or nuclei as by a stabilizing function of the cerebrum. Hitzig (1884) based his support for this conclusion on the observation that his patient with unilateral cerebellar defect suffered no inconvenience until the brain was attacked by syphilis. Vogt and Astwazaturow (1912) subscribed to the same view as they, too, found that in pure agenesis tremor and ataxia were observed only in cases with concurrent cerebral disease. To these cases one can add that of Rubinstein and Freeman whose patient showed no signs of cerebellar disorder until generalized arteriosclerosis became cerebrally widespread.

In conclusion, it may be remarked that the frequency with which some degree of hydrocephalus has been found in conjunction with cerebellar agenesis suggests that in such cases the fluid accumulation and the cerebellar deficiency may have a common origin in some embryonic defect, possibly genetically determined.

SUMMARY

A male imbecile, who at birth was noted to have a slight degree of hydrocephalus, was handicapped throughout his life by unsteadiness of gait, clumsiness of the hands and dysarthria. He died in his 55th year. Examination of the nervous system showed that the cerebellum was represented by a single fragment of tissue attached to the right side of the pons. It measured 7 mm. $\times$ 3 mm. $\times$ 1 mm.

ACKNOWLEDGMENT

I am much indebted to Dr. D. N. Parfitt for placing at my disposal the clinical notes and brain of this patient.

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A CONTRIBUTION TO THE OBJECTIVE MEASUREMENT OF THE CATHARTIC PROCESS—I

By

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I. INTRODUCTION

In previous work (8, 9) the writer has found that measures of breathing activity during speech, and of output of speech per breath are related to the emotional intensity and to the extent to which emotions are restrained or given free expression in the exchanges during psychiatric interviews. A high level of ventilation, i.e. high breathing activity with low output of speech per breath was shown to belong to content implying outgoing affect (jealousy, appetite, sex, aggression, wishes and hopes), and a low level of ventilation in speech to be associated with topics of restricted emotionality, such as fear, inhibition, deprivation, as well as to reasoning.

Tension states as rated by physicians or as experienced subjectively, as well as anxiety states and other emotional disturbances have been shown to be associated with physiological changes in the muscular system as measured by the electromyograph (15, 19, 21). Increased muscular tension was also found to accompany hyperventilation (1, 6) and increased muscular tension as well as inhibited breathing have been reported to accompany intellectual effort (11, 22, 23). Rising gradients of tension from forehead and chin have recently been shown to accompany sustained attention when listening to read material (26).

II. THE PROBLEM

It seemed desirable at this point to study how during the process of interviewing the fluctuation of speech output and breathing activity were related to the changes in the action potentials of muscular activity, and how these physiological changes were related to the content of the interview.

In approaching this problem it is well to be aware that respiration and activity in the muscle tissue are physiologically closely related events with a varying phase relation according to the effort expended. There seems to be a correspondence between the phenomena of "oxygen debt" of muscular tissue in the phase of contraction, and the reported relation between increased muscular tension and inhibited breathing. It has been argued, however, that lack of oxygen in the tissues is not the immediate stimulus which sets off the normal respiratory mechanism. ". . . in normal life we breathe for psychologic reasons before we have to breathe of physiologic necessity" (16).

In fact, little is known about the pattern of respiratory action and muscular activity in the tissues accompanying mental effort and emotion. The quantities relevant to muscle tension as distinct from movements are on a far more reduced scale, the measurements being those of sustained muscle potentials, obtained under experimental conditions of rest and exclusion of high-voltage bursts of activity produced by movement.

The purpose of the present investigation was therefore to learn how the relationship between respiratory and tissue activity may vary with different individuals, with different stages in the interview, and with different content.

III. EXPERIMENT

Seven subjects, including five patients at the Maudsley Hospital and two non-patients, were interviewed by the writer, who adopted a fairly passive role to encourage the subject to talk freely. A certain degree of guidance was, however, exercised usually when the subject had come to a pause, and there was some prodding once a topic promising display of affect was broached.

The subjects were seated at a table opposite the interviewer with the microphone between. They were requested to rest their arms on the table with hands clasped and refrain from gesturing. The interviews were recorded on the speech recorder, while the action potentials of the subjects' forearm muscles were continuously recorded on the electromyograph. Dr. P. Sainsbury, who assisted in the setting up of this part of the experiment, has described his method elsewhere (21). The muscle groups of the forearms were chosen in preference to the facial or neck muscles, as the latter were much more likely to be affected by speech movements.

Apart from the microphone which fed the tape recorder, a throat microphone was fixed round the subject's neck and the speech movements were fed into the same polygraph. Thus a record of the voice tracing ran synchronously with the muscular tension tracings, and their integrator. One pen recorded seconds and half-minutes. A signal between each 30 seconds was fed into the tape recorder, and coincided with the half-minute pen mark. There was also a signal between the interviewer and the technician which was worked whenever the subject disobeyed the instruction not to move his arms. These passages which were, however, few and short were removed from the record.

The speech recordings were transcribed, the subjects' utterances timed, the syllables in each utterance counted, and the inspirations which were clearly audible on good quality recordings (8) were also counted for each utterance. The concomitant changes of the measures were studied separately for each individual record.

The data at our disposal were as follows:

- (a) number of syllables in each utterance = N_s
- (b) total duration of each utterance in minutes = t
- (c) inspirations in each utterance = N_i
- (d) action potentials of muscular tension = AP

The following measures were derived from these quantities:

$$\frac{N_s}{t} = \text{speech rate (SR)}$$

$$\frac{N_i}{N_s} \times 100 = \text{ventilation percentage (V) or degree of ventilation in speech}$$

$$\left(\text{reciprocal of output of speech per breath} = \frac{N_s}{N_i} \right)$$

$$\frac{N_i}{t} = \text{respiration rate (RR)}$$

The action potentials of muscular tension were recorded in the following way: the integrated units were counted for each utterance and divided by the number of seconds in the utterance. This measure will be referred to as AP.

IV. TREATMENT OF DATA

To study the changing relationships of the measures described above each interview was treated separately. The data are derived from utterances following upon each other in sequence as the interview progressed. They can therefore

not be treated as random occurrences but each interview is to be regarded as a series of temporal events.

The statistical methods for analysing changes taking place over time have been largely developed by economists under the name of Time Series Analysis.

"Time series are sequences, discrete or continuous, of quantitative data assigned to specific moments in time and studied with respect to the statistics of their distribution in time. They may be simple, in which case they consist of a single numerically given observation at each moment of the discrete or continuous base sequence; or multiple, in which case they consist of a number of separate quantities tabulated according to a time common to all" (27). The time series composed of our data will be multiple ones. They will be analysed in order to arrive at an empirical description, not to provide a basis for prediction or extrapolation.

Certain assumptions underlying the analysis of time series and certain problems with which the statistics of time series are concerned derive from specific conditions connected with economic data, which are not necessarily reasonable if applied to the analysis of longitudinal data in psychology (2). Thus temporal trend, which economists will often remove as giving a spurious bias to correlations of temporal series, reflecting a general fact whose effect is misleading, is often a very interesting object of study in its own merits.

The correlation of trends signifies that there is an underlying common condition which affects both quantities correlated. If therefore for example respiration rate (RR) and muscular tension (AP) correlate, and both show a clear trend of progression at increasing rates, obviously neither RR nor AP are independent quantities but their covariation is due to an underlying condition affecting them both. Their correlation with time implies a correlation with an underlying condition changing in time, as will be seen later. This supposed underlying condition—we shall take it to be the degree of activation of the organism as it changes in the course of the interview—is the main object of interest. The correlation of AP and RR serves as its indicator; their correlation is therefore from our point of view not "spurious" but helps us to understand and serves to define the mental state as the interview progresses in terms of these quantities. Because of the non-random character of the data the term used to describe the relationship between the time series will be "covariation". Regression lines will be used to give a fit which is "the best fit" from the point of view of the method of least squares, but they will not be interpreted in terms of tests of significance.

The reciprocal innervation of biological and psychological activities (12, 18) will often mask the relatedness of two processes. Complex processes taking place in temporal sequence and involving mechanisms which dovetail can be expected to run their course with a lag of varying intervals. Each dependent process may therefore be expected to show the effect of the related process with a certain varying time lag provided the continuity of the process is not interrupted by interference, e.g. intervention of the interviewer. In the fast running stream of speech activity the mechanisms or activities we are interested in, namely muscular tension, respiration and verbalization with the accompanying thought processes move at different rates and rhythms. The electrical activity in the muscular tissue is a continuous phenomenon with instantaneous reactivity, breathing a periodic activity fluctuating in intensity in relation to effort and excitement, and the output of speech although seemingly continuous fluctuates under the influence of emotion as well as of voluntary control. These differences in the rhythms and rates of output are most relevant facts in studying the covari-

ation of these activities. The units of measurement had to have a minimum duration so as to allow for reliable rates (RR and SR) and ratios (AP). As a result of this averaging some lags might disappear while those which are consistent in their order of sequence would emerge. Such lags would probably depend on the degree in which the verbalization of the areas of tension or inhibition becomes more charged with "excitement breaking through the coordinating centres" (4), i.e. more cathartic in character. They should disappear as the various processes involved gain momentum and become synchronized in rhythmic discharge.

Consequently the question of the relation of the trends, i.e. the long-term movements of the sequences under investigation, is meaningful in the light of our problem. We ask whether there is a consistent tendency for the rate of respiration to rise as the interview progresses, and themes charged with affect enter the discussion, and whether this is accompanied by a similar tendency of the muscular tension, or by an opposite tendency, or neither. The trend values will be obtained by the method of moving averages (see p. 85), eliminating the short-term movements (cycles) which represent the non-permanent causes that are working on the time series (24).

The nature of these non-permanent causes would depend on the nature of the trend. Thus, if the trend is towards confession and abreaction, transient defences and escapes into irrelevant themes would be as non-permanent as are the deviations due to the interviewer's interference. If the trend is one of growing resistance transient bursts of emotion are to be regarded as non-permanent. We shall also be interested to see how the original quantities enveloping short-term cycles as well as long-term trends are related.

V. UNITS OF MEASUREMENT

The units of measurement are not equal time units but utterances, i.e. periods of speech lasting from a preceding question or utterance of the interviewer to the next, which is usually occasioned by the subject having come to a natural stop or pause. These may vary in length but they seem to be the natural and genuine units of conversation. Short utterances, provided they are long enough to secure reliable measurements, often reveal explosively significant and most vital states of emotion, whose intensity makes up for the duration analogous to Lashley's "whipsnapping" movements (18).

Information theory also points towards the same approach (10). In terms of the latter some short utterances may contain as much and more information as some long ones. And while our choice is not based on a quantitative measure of amount of information we have a better chance of dividing speech output according to the latter criterion using as our unit utterances emerging naturally in conversation than by using passages of speech of equal duration as measured by objective time.

VI. RESULTS

1. General

On inspection of the seven multiple time series (Figs. 1 and 2) showing the trends of respiration rate, action potentials, ventilation percentage and speech rate for the interviews recorded the following was observed. In the different interviews the above variables, and particularly respiration rate and action potentials, are differently related. Also the nature of the relation changed, in some instances, radically in the course of the interview and, as we shall see later, at significant points in the series, i.e. significant from the point of view of the content.

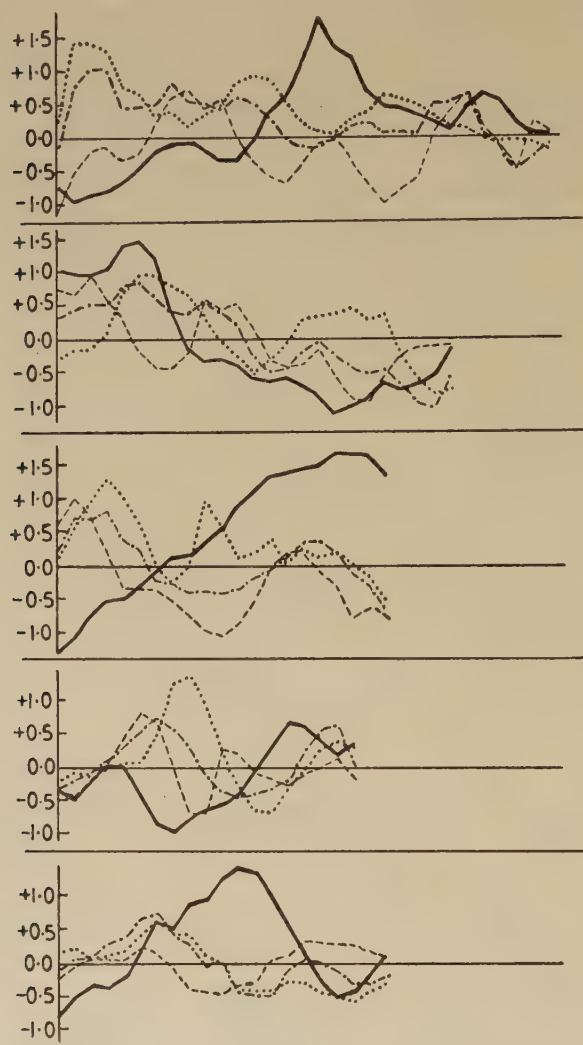


FIG. 1.—Moving average trends of multiple series of Muscular Tension (AP—), Respiration Rate (RR— · —), Ventilation Percentage (V····) and Speech Rate (SR— · —) obtained from subsequent utterances of five subjects during interviews.

Two of the interviews (S.I., B.I., Fig. 2) stand out, as may be seen from the diagrams, because they offer at first inspection a very similar profile, respiration rate, action potentials and ventilation percentage progressing towards a simultaneous peak while speech rate reaches a minimum; after the peak of the curve of respiration rate, ventilation and muscular tension these drop radically and muscular tension reaches a level below the initial one.

Of the remaining interviews two are variants of these two profiles; the rest differ in two aspects: (a) the multiple time series of measurements derived from these interviews is not so centred about a peak, and (b) the trends of respiration rate, action potentials, ventilation percentage and speech rate are not so clearly related.

As all interviews, although recorded more or less under the same external conditions, were fairly spontaneous phenomena, it seems an interesting fact

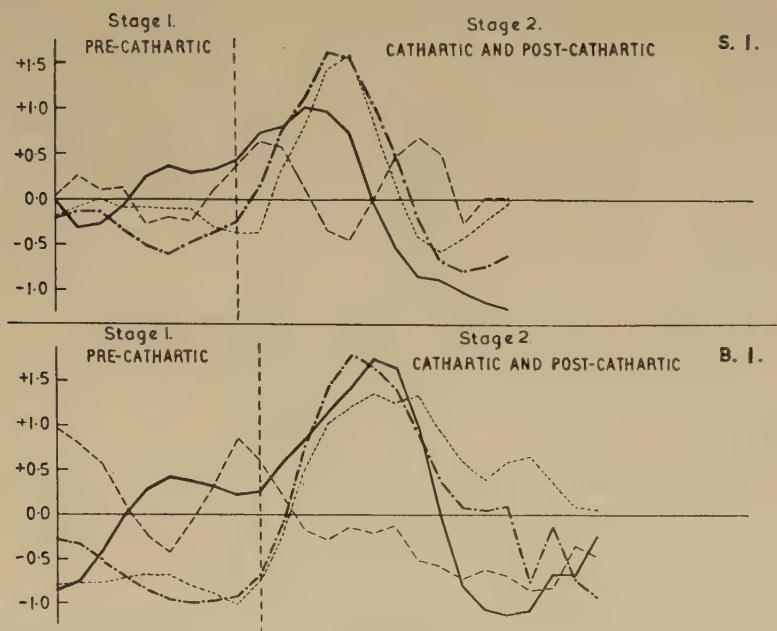


FIG. 2.—Moving average trends of multiple series of Muscular Tension (AP—), Respiration Rate (RR— · —), Ventilation Percentage (V····) and Speech Rate (SR---) obtained from subsequent utterances of S.I. and B.I. during interviews.

in itself that there should have emerged two such nearly identical profiles of speech-breathing and electromyographic measures as those of S.I. (a normal woman) and B.I. a depressed patient. This fact is the more interesting as the two profiles correspond very closely to the picture of the process of abreaction through verbal expression that may be derived from the literature. This paper will therefore concentrate on the analysis of these two records only. It will be useful before we turn to the theoretical model to analyse the two records in some detail, and see how far they represent a common phenomenon.

2. Analysis of records S.I. and B.I.

S.I. Female, 30, who volunteered for the experiment. S.I. had had some psychotherapeutic treatment, but was, on the surface, a well-adjusted individual. She was asked by the experimenter to think of a number of experiences, topics, or fantasies charged with a variety of emotions such as pleasure, anger, anxiety, joy, excitement, etc., to talk about. She reported that no other themes but aggressive ones occurred to her and suggested on her own initiative that this might have something to do with her ambivalent relation with the experimenter, in fact that the compulsive choice of the motive of aggression against women was a transference phenomenon.

The subject's record contains 25 utterances for which we have the measurements of respiration rate, speech rate, ventilation percentage and action potentials. The subject's mean values and standard deviations are given in Table I. Fig. 3 shows the four measures for comparison transformed into sigma scores as they progress from utterance to utterance. Utterances of less than 40 syllables were not included. The total duration of the 25 utterances was 15 minutes, and their mean length 161 syllables ranging from 61 to 539 syllables.

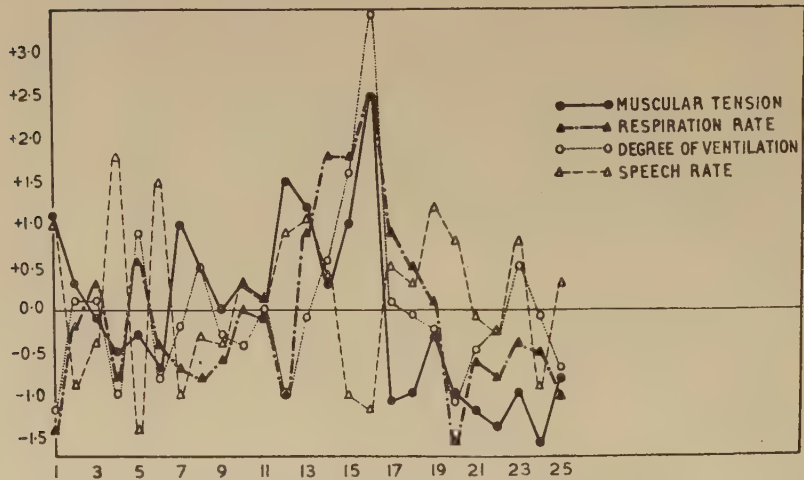


FIG. 3.—Standard scores of Muscular Tension (AP), Respiration Rate (RR), Ventilation Percentage (V), and Speech Rate (SR) for series of 25 utterances in interview of S.I.

TABLE I

Means and Standard Deviations of SR (Speech Rate), RR (Respiration Rate), V (Ventilation Percentage), and AP (Action Potentials of Muscular Tension) for subjects S.I. and B.I.

		Means	S.D.
SR	S.I.	4.3	0.78
	B.I.	2.3	0.81
RR	S.I.	7.5	1.80
	B.I.	7.8	3.00
V	S.I.	3.1	0.98
	B.I.	6.2	3.15
AP	S.I.	3.4	1.30
	B.I.	4.4	1.64

Action Potentials are not strictly comparable as the calibration of the apparatus could not be kept constant.

As mentioned before the rate of respiration (RR), muscular tension (AP), and the ventilation percentage (V) all progress, with a varying degree of fluctuation, towards a peak. The speech rate (SR) fluctuates in the first stage of the interview, in large cycles inversely to respiration rate and ventilation percentage. Increase in speech rate in this initial part of the interview is therefore achieved by a decrease in breath rate. In the next part of the interview after the interviewer has broached the theme of the subject's aggressive phantasy, which is followed by a sharp rise in the subject's muscular tension (utterance 12), there is a steady rise in speech rate (utterances 11–13). This continues while the respiration rate remains at a lower level. The speech rate recedes (utterance 14) after the sharp rise in respiration rate, and the synchronous mounting of respiration rate, ventilation percentage and muscular tension coincides with a trough in the speech rate (utterances 15–16). The peak of the interview (utterance 16) as emerging in the movements of the respiration rate, ventilation percentage and muscular tension lines and the trough of speech rate accompanies an explosive

utterance by the subject giving vent to a phantasy of extremely aggressive content.

Fig. 2 (top) presents the same sequence smoothed by moving averages of three subsequent utterances. This record shows clearly that, disregarding an initial point of somewhat higher tension, there is a fairly steady and slow rise in the tension state, the curve reaching its peak with the aggressive phantasy, and that after the peak there is a consistent but considerably steeper drop in the tension state to a level of relaxation which is considerably below the initial tension state.

The sequence of respiration rates accompanying the tension sequence shows stability in the first stage of rising tension (Fig. 2). As Fig. 3 shows there is a clearly decreasing trend between utterances 2 and 9. In the second stage the trend line of respiration rises steeply together with muscular tension, and descends more gradually. On the smoothed curve of moving averages this appears in the form of a shift in the crest of the curve of respiration. In fact, its true peak is in the same utterance as that of tension, as may be seen from Fig. 3.

The initial period of rising tension is thus accompanied by a slightly restricted breathing rate—whereby the two upward cycles of AP with peaks in utterances 7 and 12, are countered by downward cycles of RR. We also see (Fig. 2) that up to the point of change in the slope of RR the speech rate maintains its level. The same may be said about the ventilation percentage, with the difference that the latter retains its constancy with less fluctuation and for longer, rising from its preferred level by two utterances later. Its balance is maintained for so much longer by virtue of the rising speech rate, as the figure shows. This behaviour of the ventilation percentage (V) is in accordance with our hypothesis concerning its psychological significance (8); namely that it is a measure of balance or control maintained by virtue of speech activity, notwithstanding a certain excitation of the neuromuscular and autonomic systems.

A more steady and radical decline in speech rate from utterance 14 to utterance 16 coincides with the synchronous volley of AP, RR and V (Fig. 3).^{*} It recovers a relative balance after the final and simultaneous drop of these three variables.

B.I. A depressed patient of good intelligence given to bouts of weeping, agitation, feelings of exhaustion, inability to cope and futility. The diagnosis was one of affective disorder—manic-depressive psychosis. She responded well to treatment by E.C.T.

This subject's record contains 29 utterances of sufficient length to yield reliable measurements of RR, SR, V and AP. The mean values and standard deviations are given in Table I. Fig. 4 shows the four measures in sequence of time. Again utterances of less than 40 syllables were not included. The total duration of the 29 utterances was 19 minutes and 15 seconds, and their mean length was 89 syllables ranging from 42–255 syllables.

As in the record of S.I. the rate of respiration (RR), muscular tension (AP), and ventilation percentage (V) progress, with a varying degree of fluctuation, towards a peak. Speech rate fluctuates rather more violently about the mean up to utterance 14 which also marks the beginning of the rise to a peak of respiration rate, muscular tension and ventilation, and from thereon speech rate fluctuates about a lower level (about one sigma below the mean). The initially decreasing trend of the speech rate (SR) accompanied by the decreasing trend of the rate of respiration (RR), and increase of muscular tension (AP) comprising the first utterances up to number 8, in which the subject discusses her

^{*} There is no mechanical relation between respiration rate and speech rate.

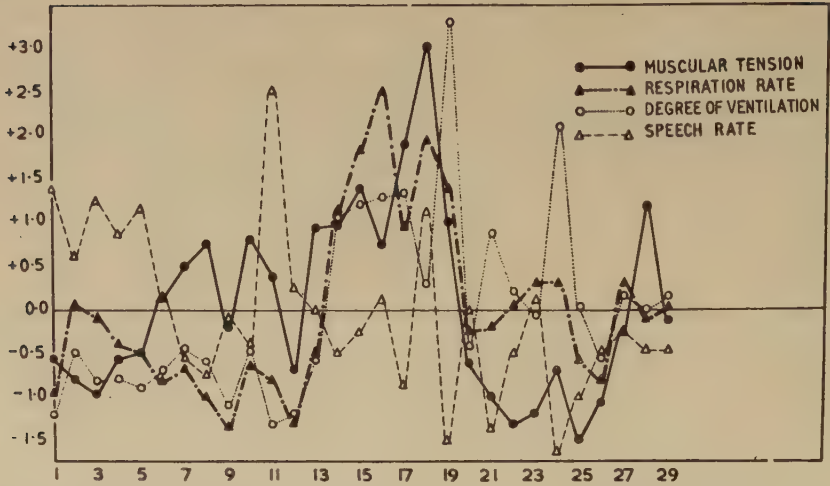


Fig. 4.—Standard scores of Muscular Tension (AP), Respiration Rate (RR), Ventilation Percentage (V), and Speech Rate (SR) for series of 29 utterances in interview of B.I.

father's physical and mental illness, pass into a fairly stable condition with RR, V and AP keeping an even keel, while the speech rises steeply. In these utterances (8–11) the topic changes from the father's to the patient's own condition, of which she gives a descriptive and rather detached account in general terms. After utterance 11 the interviewer asks her to give a more specific and concrete example of her experiences. The patient still tries to describe, rather than produce material (utterance 12). Continuing (utterance 13) she comes to remember a certain event and hesitates. At this point her muscular tension rises steeply, accompanied by a rise in breath rate (RR) and in ventilation (V), and a drop in speech rate (SR). From there on the subject brings out, with much hesitation and under continuous prodding by the interviewer, the story of her father's suicide and discusses her resistance to telling the story (utterance 13). The interviewer prods the patient to tell her thoughts on finding her father while he was lying under the gas oven (having tried to commit suicide) and the patient confesses guilt feelings (utterance 15) and elaborates in utterances 16 and 17 on them. This part of the interview is accompanied by rising tension. In utterance 18 she blurts out that her father's suicide had seemed to her desirable, in some ways. In utterance 19 the patient admits fear of her father. At this point the speech becomes extremely hesitant (slow) and while the respiration rate drops a little from utterance 18 the ventilation percentage reaches its peak. The muscular tension drops simultaneously and continues from this utterance on to do so consistently, descending by a steep slope to a new low level of muscular tension below the initial level. At a slow rate of speech (low SR) and with a considerable degree of ventilation the patient now volunteers how her husband reminds her of her father, being as unsatisfactory as the latter (utterances 20, 21, 22) and how she felt guilty about making demands on both (utterances 23, 24). There is a long pause (11.6 seconds) after this utterance, perhaps indicating that the momentum of the series had come to an end. The interviewer introduced a new subject (of how the patient met her husband) and from there on we can observe a gradual re-activation of the whole system (AP, SR and RR rising again), the theme of this passage being the patient's marital relationship. It evolved to a point when the patient described her doubts

about her feelings towards her husband, but as the interview had already lasted long enough this theme was not pursued.

3. *Comparison of records S.I. and B.I. in terms of the relation between their respiration rates and muscular tension*

In comparing the two records (S.I. and B.I.) it is interesting to observe that in both the system, as represented in the form of speech-breathing and tissue activity, enters the excitatory phase when the interviewer insists that the subjects should proceed from talking *about*, to talking *of* their experiences, i.e. to producing the actual material. Utterance 12 in S.I. and utterance 12 in B.I. mark this event.

The data of breath rate and muscular tension (RR and AP) in both records were therefore divided into two groups: For S.I. measures for the first 12 utterances before the steep rise of RR from six to ten respirations per minute were included in the first group. The second group of data comprised the subsequent 13 utterances covering themes such as the subject's phantasy of aggression against a woman rival, revealed hesitatingly at first and under the interviewer's prodding gaining momentum and final expression, and including the subsequent sequences of conversation which followed the discharge. Their content were attempts on the subject's part to discuss aggressive feelings against men. According to the subject's own observation, however, these were abortive, "... they turn into something sweeter".

For B.I. the first 11 utterances (1-11) before the rise of RR from 6.3 to 11.4 respirations per minute, contain descriptive accounts of her father's and her own condition. These were included in the first group of data. The following utterances are again responses to the interviewer's prodding and her insistence on actual material. Resistance passes into hesitating production of material (fear of father) at first without expressing emotion (AP and RR rising all the while), and eventually expressing emotion (fear of father and guilt admitted) and discharging tension. In the utterances following discharge the patient volunteers associations leading from her father to her husband. These utterances (from 12 to 24) are included in group 2. The material about the subject's marital relationships are not included as it is part of a new sequence introduced on the interviewer's initiative.

Regression lines were calculated for RR and AP (raw scores) of groups 1 and 2 separately for both S.I. and B.I., and Fig. 5 shows that they are in inverse relation to each other. The rising muscular tension in the first part of both interviews is accompanied by a steady maintenance to slightly decreasing level of respiratory activity ($AP = 9.87 - 0.61 RR$ for S.I. and $AP = 5.78 - 0.30 RR$ for B.I.).

In the second part, again in both interviews, the respiration rate follows the rise and fall of muscular tension ($AP = 5.22 + 1.16 RR$ for S.I. and $AP = 0.23 + 0.47 RR$ for B.I.).

Figs. 3 and 4 also illustrate the principle of asynchronous flux (5, 17) in the various responses interacting in the course of the initial stages of the interviews. This picture passes rather dramatically at utterance 12 in S.I. and 14 in B.I. into one of synchronous activation of speech-breathing behaviour and muscular tension.

At the same time, if we group our data without reference to the dynamic aspect of serial order and compare the action potentials of muscular tension for states of low, medium, and high breathing activity we again obtain very comparable results for the two interviews, as may be seen from Table II.

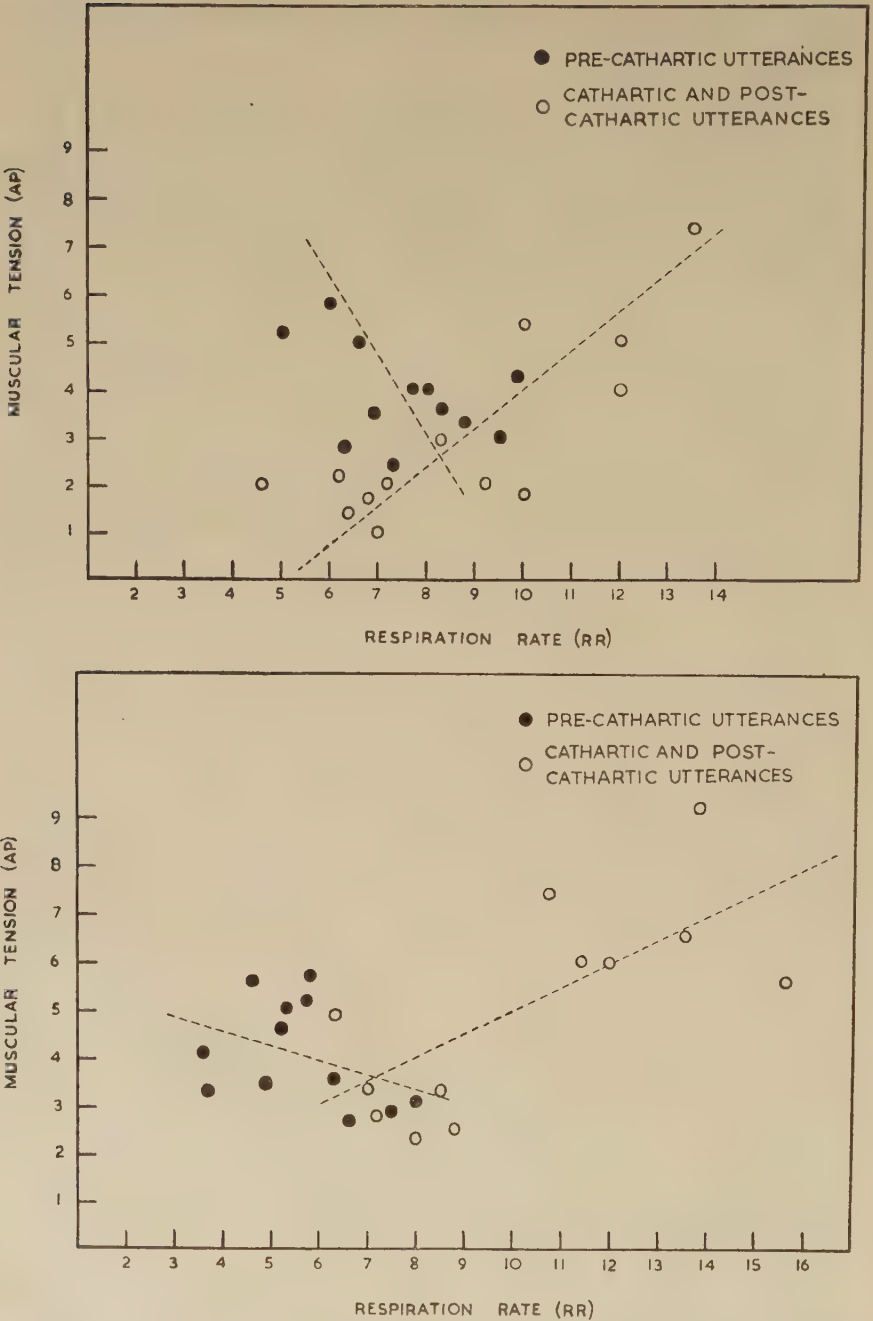


FIG. 5.—Regression lines for AP and RR (raw scores) of pre-cathartic, and cathartic plus post-cathartic utterances for S.I. and B.I.

From Table II we can see that reduced breathing activity accompanied, in these records, a state of increased tension, that a moderate or normal rate of breathing was associated with a relaxed condition of the muscles, and that a high breath rate accompanied states of high muscular tension. This was more

pronounced in the case of B.I. whose gradient of rising tension was considerably steeper than that of S.I. It might be recalled that B.I. was a patient and S.I. a normal woman. There is besides the fact that there were only three utterances with reduced breathing (less than 6.0 p.m.) in the record of S.I. The actual values were 5.8, 5.2 and 2.0 respirations per minute.

TABLE II

Means and Standard Deviations of action potentials of muscular tension (AP) for utterances of low, medium, and high respiration rates for subjects S.I. and B.I.

Respiration Rates			Mean	S.D.	N
x . . . less than 6.0 p.m.	..	S.I.	4.00	2.36	3
	..	B.I.	4.36	0.97	10
y . . . 6.0-9.0 p.m.	..	S.I.	2.84	1.10	14
	..	B.I.	3.47	1.06	16
z . . . 9.0 p.m. and more	..	S.I.	4.11	1.75	8
	..	B.I.	6.41	1.49	7

F—ratios:	S.I.	F=2.62	n.s.		
	B.I.	F=14.81		dfs.=2 and 30	P=0.001
		t_{xz} = 3.47		P=0.001	
		t_{yz} = 2.56		P=0.02	

An analysis of variance was carried out on the means of action potentials in the three respiration groups for each subject and Table II shows that the F ratio was highly significant in the case of B.I. but did not quite reach significance level in the case of S.I. T-tests were carried out for B.I. to see which of the groups were mainly responsible for the differences. The significant differences were between the group of utterances spoken at a rate of 9.0 and more respirations a minute (hyperventilated group), and each of the two other groups.

Although this time our data were grouped without consideration of any chronological order, according to degree of breathing activity as measured by respiration rate, there is an obvious link between the stages of the cathartic process (pre-cathartic, cathartic and post-cathartic) and the levels of respiratory activity. The utterances spoken with a reduced breathing rate belong to the pre-cathartic section of the series, those uttered at a very high rate of respiration constitute the crest of the curve (section of discharge or catharsis), and the utterances in which breathing was relatively normal came after the apex, when tension had relaxed to a very low level (post-cathartic section).

4. The Cathartic Loop

Figs. 6 and 7 present the function that holds between respiration rate and muscular tension (AP) as it evolves in sequential order of utterances in the course of the interview. To eliminate all non-permanent changes and obtain clear trends moving averages of moving averages were calculated all based on three items. By this the curves were smoothed without allowing distant items to influence the values. The resulting dots on the diagram were then connected by a line following the order of the utterances to which they belonged as these occurred in the interview.

The resulting curve shows that from the beginning there was a steady rise in muscular tension while breath rate remained either constant (S.I.) or decreased (B.I.). Towards the end of this stage there was a static period lasting four and five utterances respectively in which neuromuscular as well as respiratory activity remained more or less unchanged, and this was followed by a break-

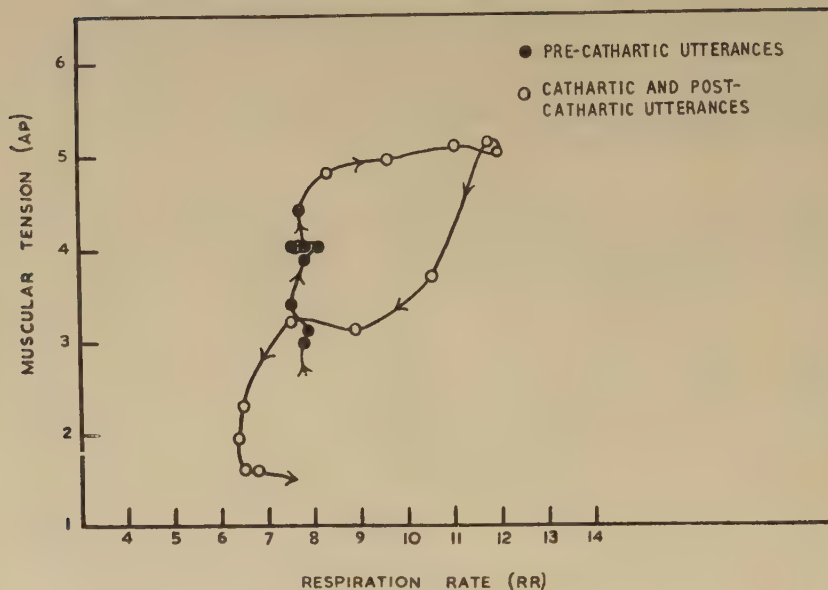


FIG. 6.—Function holding between RR and AP for subsequent utterances of S.I. Arrows indicate order of sequence in time.

through, with both variables, respiration and muscular tension, rising. The function then reached a point of maximal activity which at the same time was the turning point in the movement of the curve, taking the shape of a loop, and from thereon both muscular tension and respiration rate decreased. The curve of return, however, does not coincide with the rising curve but descends in a far steeper slope. If we look upon the three directions which the function takes during the process as the three sides of a right-angled triangle, the curve reaches the starting level of activity by the direct route of the hypotenuse.

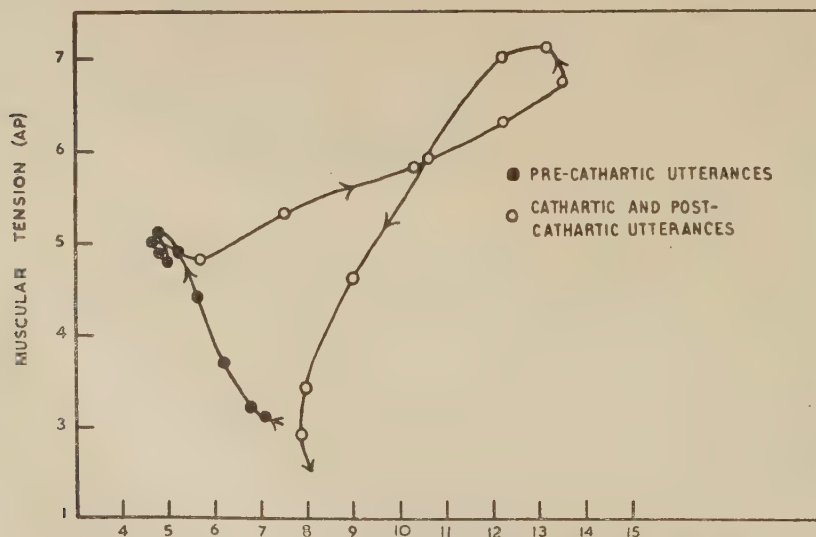


FIG. 7.—Function holding between RR and AP for subsequent utterances of B.I. Arrows indicate order of sequence in time.

We have seen from the time series that the arousal of the respiration rate lagged behind that of muscular tension, and the loop-curve is the characteristic of a function in which the effect lags behind the cause. We are reminded of the hysteresis loop representing the relation of magnetic induction and the magnetizing force in a ferro-magnetic substance, and showing how the former lags in effect behind the latter.

The three stages in the two interviews discussed, represented by the different functional relationships of the neuromuscular and respiratory activities as measured, have thus been shown in evolution.

VII. DISCUSSION

The chance occurrence of two nearly identical profiles of interview measurements among seven sets of measurements, each for a different individual, calls for an explanation. What is the factor or factors, or condition common to the interviews S.I. and B.I. which is not equally shared by the rest?

As we could not repeat the interviews with the same person we do not know whether it is a personal one. From the personalities of S.I. and B.I. we may make some speculative observations. Although S.I. is a normal person and B.I. a patient, both women are classifiable as cyclothymes. B.I. is a manic-depressive capable of affective discharges with a great deal of weeping. S.I. also discharged affect readily in speech, though her way of ventilating excitement during speech was laughter. The rest of the subjects in the experiment included one schizoid personality with difficulties of concentration, one depressed patient with symptoms of hypertension, one case of a depressive reaction in a compulsive personality, one non-patient undergoing analysis for character neurosis with anxiety symptoms, and one atypical case of anorexia nervosa. The only criterion determining the selection of these subjects for the experiment was that of their verbal capacity.

S.I. and B.I. also resembled each other in their positive response to the interviewer's prodding in traumatic areas after initial resistance. Three steps may be distinguished which are common in the process of both interviews:

(a) In both interviews the subject's attention became focussed on a central problem, a traumatic theme, partly in the course of the subject's conversation as a result of free association, but then developed as a result of the interviewer's questioning and prodding.

(b) A period of *dénouement*—in psychoanalytic terminology "working through the material"—followed this opening, and

(c) This *dénouement*, varying in complexity, dependent on withdrawals and interspersed resistances, eventually led to a relatively unreserved, even explosive, verbal expression of the disturbing content with discharge of tension, i.e. to "catharsis".

The impact of focussing a subject's attention on a traumatic theme seemed to be this: that his tissue activity was activated first and breathing activity was restrained. At this stage with the content remaining peripheral speech accelerated (utterances 7-12 for S.I. and 8-11 for B.I.) with a relatively poor level of ventilation (high SR, low V): as the crucial content was focussed (12 for S.I. and 14 for B.I.) and RR leapt up, SR in both interviews slowed down and became highly ventilated.

The two series (S.I. and B.I.) are of particular interest because they reflect in terms of objective measures a sequence of events closely corresponding to what in the literature has been described as the process leading to catharsis or "abreaction".

The general assumption underlying all psychotherapy is that beneficial effects are obtained from talking out, or ventilating in speech, traumatic experiences. Freud's original formulation of this assumption stresses that verbal expression must be given to affect. "Recollections without affects are almost utterly useless. The psychic process which originally elapsed must be reproduced as vividly as possible so as to bring it back into the *statum nascendi*, and then thoroughly "talked out". Breuer and Freud (4, 5) came to the conclusion that it is of great consequence whether there was an "energetic reaction" to the affectful experience or not. "By abreaction we understand a whole series of voluntary or involuntary reflexes, ranging from crying to an act of revenge, through which according to experience affects are discharged. If the success of this reaction is of sufficient strength it results in the disappearance of a great part of the affect. Language attests to this fact of daily observation, in such expressions as 'to give vent to one's feeling', to be 'relieved by weeping', etc. If the reaction is suppressed the affect remains united with the memory."

The authors close the introduction to their "preliminary notes" with the following remark on psychotherapy:

"We can now understand in what manner the psychotherapeutic method propounded by us exerts its curative effect. It abrogates the efficacy of the original non-abreacted ideas by affording an outlet to their strangled affects through speech."

From the writer's previous studies of speech output in relation to breathing during speech (8, 9) it has become evident that the term "ventilation" or giving "vent to one's feelings" carries more than a metaphorical meaning. The measures of breath rate during speech in conjunction with the measure of output of speech (number of syllables) per breath were, as mentioned before, found (9) to be reliable objective indicators of the degree of emotional intensity and of the extent to which emotions were restrained or given free expression in the exchanges during psychiatric interviews.

It was shown that the higher the ventilation percentage (V) is the lesser the efficiency with which the respiratory activity was transformed into verbal activity. The degree in which the V remains constant through the fluctuations of the respiration rate (RR) shows the extent to which balance is maintained by virtue of increased speech activity, i.e. it shows the extent of control or affect or of defence against affect through speech, or the degree of its ventilation or uncontrolled discharge.

We therefore seem to have in V the objective corollary to what Freud and Breuer seem to have had in mind when they used such terms as "verbal expression of affect", or giving "vent" or "outlet" to one's feelings.

The rate of respiration during speech was shown in the previous study (9), in which validation was undertaken against content, to measure the intensity of emotional expression or repression of affect. Outgoing affect was shown to manifest itself in increased breath rate, excitement in high breath rate, whereas repressed affect, attention, caution, and fear was shown to be revealed in inhibited breathing. Breuer and Freud's "strangled affect" would belong to the last category.

The beneficial effects expected from the "verbal expression of affect" are usually described as release of tension. Apart from considerable evidence (15, 19, 21) to the effect that states of emotional tension and anxiety are accompanied by rising electrical activity in the muscles (muscle tension) as measured by the electromyograph, it is clear from the literature that discharge of tension has been conceived by psychoanalysts as a relaxation of the muscular tonus. Thus

W. Reich holds that "the rigidity of the musculature is the somatic side of the process of repression, and the basis for its continued existence" (20). He also stresses the connection between muscular tension and respiration. Reich holds that inhibition of respiration is the physiological mechanism of the suppression and repression of emotion, and consequently the basic mechanism of the neurosis in general.

The breaking through of this "muscular armour" of resistance and character attitudes is envisaged by the same author as determined by the amount of "vegetative energy" (respiration) accompanying the process. While Reich may in the view of orthodox psychoanalysis be over-emphasizing the role of the vegetative energy, it is obvious from the remarks made by Breuer and Freud that they postulated for the discharge of tension a high degree of vegetative energy accompanying the process of verbalization.

With the measures of speech-breathing activity (RR, V and SR), and muscular tension (action potentials as measured on the EMG), it becomes possible to construct a model of how the process of catharsis and abreaction takes its course, according to psychoanalytic theory and in harmony with some dynamic principles of neuro-physiological action which seem relevant to the speech process. These are the principles of temporal integration in sequences of actions which are involved in language and speech as in other skills.

In terms of psychoanalytic theory a traumatic theme coming up for discussion would at first be prevented from being ventilated in speech (stage of defence) by repression or suppression which we expect to manifest itself in increased muscular tension and decreased respiration. As the material would enter the "working through" phase resistance and tension should increase together with increasing excitation or, as Freud (7) calls it, with "a quantitative increase of pressure" of which "unpleasure . . . would be the perceptual sensation". As the verbalization of the areas of tension or inhibition becomes more charged with excitement the latter breaking through the co-ordinating centres (4, 5), i.e. as utterance becomes more cathartic in character, the "asynchronous flux" (17) of the various activities measured (speech output, respiration, muscular tension) characteristic of "the state of dynamic equilibrium" (4, 5), will gain momentum and they will organize themselves into a pattern.

With the synchronous rise of expressed affect (respiration and ventilation) and tension (AP) the maximal point in the sequence will be approached and the discharge should be in the form of "synchronized and rhythmic volleys" (16). After this the muscular rigidity should be broken, and the affect should subside. A similar picture emerges from Hughlings Jackson's (14) description of emotional speech. "Emotion appropriates and subordinates an intellectual utterance. . . . We see in the utterance itself that with a fall in the intellectual there is a rise in the emotional one. There may be an equal, no doubt a greater, liberation of energy during these utterances, but it is directed more strongly on the vocal (including respiratory) organs, i.e. to those organs which serve especially during emotions."

On the physiological side this phenomenon has been described by Hoagland (13) under the name "relaxation oscillator". This type of oscillation depends upon a discharge taking place when some limiting potential or intensity is reached. "Its essential nature is (a) that some state, some potential, some intensity is built up by a continuous process, and the condition becomes less and less stable until one is reached in which discharge must take place, and (b) this discharge once started forms a path for itself by which (as in a siphon

or electric arc) further discharge is facilitated until what has been built up gradually has been broken down and the process begins again."

The temporal sequence of the process reflected in our measurements corresponds very closely to the above descriptions. Considering that the content also points in the same direction it appears that the two profiles S.I. and B.I. represent objective illustrations of instances of the cathartic process.

While we do not yet understand the conditions which determine the appearance of the cathartic picture in terms of objective measurements of the interview process, the fact of this close correspondence to the theoretical model constructed on the basis of the writings of the originators of the concept of catharsis through verbal expression in the interview situation seems of some significance. By demonstrating that abreaction through verbalization of emotive themes is a measurable process a step has been taken towards the study of the process of catharsis or abreaction through talking, and of the conditions which may favour or bar its evolution.

There is no mechanical relation between respiration rate and speech rate.

VIII. SUMMARY

The covariation was studied between the fluctuations of speech output, breathing activity and the action potentials of muscular tension during the process of interviewing. These changes were also related to the content of the interview.

Seven interviews were recorded on the speech recorder and measures of speech rate (SR), respiration rate (RR), and a measure of ventilation in speech (V) were derived. These measures had previously been shown to be significant as indicators of states of affect and tension. Electromyographic measures were also taken from the subject while he (or she) was speaking.

Each interview was treated separately and regarded as a series of temporal events. Time series were plotted based on the individual utterances as well as on moving averages of sequences of utterances representing the trends in the changes which took place over time.

In the different interviews the above variables and particularly respiration rate and muscular tension were differently related.

Two of the interviews stood out being nearly identical in the shape of their curves. They are analysed and discussed in detail in this paper.

The sequences of measurements were divided into two sections, pre-cathartic, and cathartic plus post-cathartic. A reversal in the relationship between respiration rate and muscular tension as expressed by regression lines was observed in the second part of both interviews. The rising muscular tension in the first part of both interviews was accompanied by a steady maintenance or slightly decreasing level of respiratory activity. In the second part, in both interviews, the respiration rate increased and decreased together with muscular tension.

The data were also grouped without consideration of any chronological order, according to level of respiration rate, and there was an obvious link between the stages of the cathartic process and the levels of respiratory activity. The lag in the arousal of respiratory activity following behind that of muscular tension was illustrated by the loop-shaped function which showed the three cathartic stages in evolution.

The relevance of these relationships to the principles of the asynchronous flux of dynamic equilibrium, and of the rhythmic synchrony of discharge was discussed.

The similarity in the pattern of measurements for the interviews was also considered in the light of the content of the utterances from which the data were derived, and it proved meaningful when compared with the theoretical picture of the "cathartic process" as described in the literature.

Suggestions were made on the basis of content analysis about factors in the structure of interviews which might be favourable or bar the unfolding of the process of catharsis.

It was concluded that abreaction through the verbalization of emotive scenes has been shown to be a measurable process, and that thereby a significant step had been taken towards the study of the process of catharsis or abreaction through talking.

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FACTS AND FICTIONS IN THE STUDY OF CHILD PSYCHIATRY*

By

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I BELIEVE that it is customary for an address from the chair not to direct attention to some particular enquiry that has engaged the speaker, but to make a general survey of the broad issues of a society and its discipline, to take a bird's-eye view of the development of the subject, or to take up some fundamental issue or issues which at the moment have reached something in the nature of a turning point.

When the practitioners of an art or science feel themselves to be at the crossroads which point to different directions, along one of which the most fruitful developments are to be found, they should pause. For myself, I think that we are at some such crossroad at the moment in the study of child psychiatry, which derives its data from many sources. Indeed, the multitude of sources—general medical, psychological, neurological, sociological, psychopathological may easily lead the purist in his own field to interpret the data of child life in terms exclusively of his own inclination and training. He will select his own facts and thereby create his own fictions. He may select his facts with all honesty for the proving of hypotheses. Indeed many hypotheses are heuristic fictions, many fact-finding mechanisms are themselves created by the hypotheses, which can be satisfied either by statistical checks or through deductive reasoning from incontrovertible facts or, better still, from the study of events which all bona fide observers can share.

I said we can regard ourselves as being at the crossroads since recent advances in various fields tend to converge because of the basic biological process which all these advances imply. The psychopathology of the child, or more broadly the development of the child and its vicissitudes in the life of the family and the society of which the family is a part, touches upon the problems of its basic needs and their field of satisfaction. These are biological issues which are entangled in the recent work on instinct and higher patterns of behaviour. The fact is that in this field, the field of ethology; the work in progress suggests divergences which should give pause to those who attempt to crystallize in psychopathological terms the meaning and destiny of the instincts which appear to form or provide the substrata of all future complex conduct. The work of Tinbergen and Lorenz on Innate Release Mechanisms is being questioned by such workers as Lehrman and Hind, who claim an absence of neurological evidence for such specific mechanisms. It may be a far cry from the moorhen and the herring gull to the human infant, but if we employ biological terms such as Instinct, there should be some agreement as to basic assumptions. If we assume that a fundamental drive such as libido undergoes development, we must ask ourselves whether or not learning or modifiability is not the better concept of a process that yields clearer understanding than the concept of libido which is a fiction presupposing a datum which is not itself modifiable but only capable of displacement or deflection. What may be styled the

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embryology of behaviour may help us to collect facts, or better still to watch events. Facts are modifiable by the observer for they are more abstract than are concrete events, and it is surprising how readily we take such facts and incorporate them into our fictions so that the latter begin to resemble facts and come to be traded as such. Tinbergen and Lorenz have made a brilliant collection of observations on animal behaviour, but the former has defined instinct in such a way that a specific neural mechanism and its alleged energy has been posited in the absence of evidence of a neurological substrate that could carry its weight. In terms of actual behaviour stated embryologically, the feeding mechanisms of birds are forced to have separate components each of which has a discrete pattern, such as the head extension, the closure of the beak and the act of deglutition. Each exist separately and aimlessly in embryo. For example, the amniotic fluid swallow reflex exists by itself. It is the environmental stimulus which alone brings them together in the purposeful act of feeding or being fed. If so simple an oral pattern is composite and made of disparate elements, how can we speak freely of an oral endowment without admitting its dependence upon learning occasions?

There are many other early mechanisms of behaviour which are built up of elements which are subject to patterning under environmental signals, which are not always available, and which are only responded to when the elements themselves reach a level of maturation before they can be utilized and before we can assign a meaning to them. In the same way the neural mechanisms have an overall unity, but an embryological disparity, so the acts of early awareness are themselves operating in a partial manner and the so-called Ego must consist of a series of nuclei before these assume their place in a common act of overall awareness. Any so-called object relationship which the infant establishes must in the first place be not with part objects of perception, but with fragments of perceptual activity arising from different and not from a yet unified source. True the organism is one, but the nuclei can be said to exist in a kind of common plasmodium, and there are still a variety of short term ends to early behaviour. Furthermore, the development of the central nervous system shows a procession of events with creative potentialities, not appearing at once but accumulating in time and space which call up these potentialities and make them kinetic at the appropriate time, but not before. To attempt to call them up sooner in order to support a doctrine of psychic structure is to present a fictional unity of apperception before the conditions necessary for its operation are brought into being. If, therefore, we assume that objects of apprehension exist in the infant of six months, we ought to present the evidence for their existence at that given moment of time and not to argue retrospectively that such and such constructs appear in the growing child and the adult whose verbalizations give ground for inference as to what exists at that time. For it is at the time of verbal analysis that the mind has whole functional relationships or parts which already had some specific function in the satisfaction of basic needs. The extraordinary fruitfulness of the analytic technique has put a strain upon us all because of the welter of data it has laid bare. Having made known a multitude of events and their relationships, which support Freud's basic hypotheses, they have made some people very impatient to bridge the gap from known to unknown. This has led to an over-zealous clinging to preliminary hypotheses and to a resorting to purely deductive reasoning—a danger to all sciences with the exception of mathematics and its sister disciplines.

It can be added as an aside that even in the establishment of such a deductive science as Geometry, it took 300 years from Thales to Euclid to

establish by experiment the fundamental principles from which the later deductive procedures could expand.

Before, therefore, we can proceed to build up a consistent yet elastic system of child development, we must accumulate data which are in the nature of events, which are observed by exterior studies checked by the insights we have gained from the interior studies of the child and the adult in analysis and in play behaviour. It might be said in defence of psychopathological data that what is opined is derived from facts. Many of these so-called facts are abstractions derived from deduction on the basis of the logical principle that a fact is whatever can be expressed in a proposition. But many such a hypothetical fact and proposition can be constructed from premises which are mythological or fictive. Many of these fictions derive from the subtle tendency of confusing the *Substantive* with *Substance* and to turn adjectives into nouns. This results in the reification of states of mind. It is true enough that the child, and later even the adult, seeks satisfactions and reductions of tension from relations with objects, many of them fragmentary—many of them fleeting or undergoing organization with change of meaning under the process of maturation itself. It is true we cannot avoid in experience the use of fictional or imaginal mental elements. As Vaihinger says in *The Philosophy of As If*—"The organism finds itself in a world of contradictory sensations; it is exposed to the assaults of a seemingly hostile external world and, in order to preserve itself, it is forced to seek every possible means of assistance, internal as well as external. In necessity and pain mental evolution begins, in contradiction and opposition consciousness awakes, and man owes his mental development more to his enemies than to his friends." This was written, I believe, independently of a knowledge of the findings of psychoanalysis, which has substantially confirmed Vaihinger's view. Melanie Klein has done much to disclose these processes in early mental evolution, but she seems to have adopted the child fictive thinking herself, raising larval incommunicable states to the level of objective certainty. It does not follow that because the child thinks in terms of fictions these fictions are facts in a universe of discourse. For when all is said and done the organism is from birth onwards subject to the correcting influences of external perception, that conditioning starts immediately and the various zones of intense affect-laden awareness are moulded from without as well as elaborated from within. Moreover, the perceptual apparatus which is the substrate of ego development arises from discrete centres, or, as Glover asserts, nuclei, and these remain discrete for a long time, so that the true object of appreciation does not seem possible and cannot therefore become centres of reference for assigning the attributes of *good* or *bad* which belong to moral ideations. To assert that it *is* so, suggests a level of ego development for making larval propositions (i.e. P is Q). The infant's behaviour can at most only be described "as if" it were making such propositions. The capacity to form the construct subject-predicate-object is a linguistic endowment. Although the child probably recognizes signs for picking up the favourable and unfavourable in a welter of stimuli assaults, it cannot on neurological grounds alone react to them adequately, let alone respond to them even in terms of some internal order. Even this internal quasi-order is a blind and groping experience; it is an archipelago of discrete forces and not a mapped-out continent. This, of course, is not to deny that there is an organic unity to begin with—but it is a far cry from such organic unity to a psychic unity. To quote Coghill (*Anatomy and the Problem of Behaviour*), "in *Amblystoma* the primary and secondary olfactory centres are relatively advanced in differentiation before the olfactory

nerves enter the brain; conduction paths from optic centres to the brain stem can be recognized before the optic nerve approaches the brain. The order of development of the conditioning system is therefore from centre to sense organ." "Comparative embryological studies indicate (he adds) that the higher the animal in the order of intelligence, the more the neural overgrowth as regards the immediate possibility of behaviour involves the conditioning mechanism; that is to say the mechanisms that determine the time and degree of the performance as opposed to the mechanisms that determine the form of the behaviour." In other words, while the growth of the nervous system promises high potentials of behaviour, we cannot assume the already ripened ego development which recent theories in psychopathology suggest. To suggest that the child, well within the first year, appreciates distinctions of good and bad is to suppose a unity of apperception which it can hardly possess. To argue backwards from adult analytical finds (which are not in dispute) is to underestimate the time factor and the elaborations which have occurred in virtue of this factor. Furthermore, it presupposes an ego whose perceptual apparatus needs a high degree of unification to function.

Still further, much has been made of the function of introjection and projection in terms of oral and anal activity. Here again there appears to be an unwarranted jump from physiological ingestion and rejection to the functions of mental assimilation. At most it is a simile, and therefore a fiction which has heuristic value and not the basis for a consistent psychological universe of discourse. Terms, or better still experiences of the child's infra-linguistic world cannot be lightly equated with terms used in adult highly differentiated language discourse and as Mrs. Brierly stated: "We must keep clear in our minds the difference between a primary simple affect and the complex emotional attitudes of later life."

A man who tried to use a different sign token every time he wished to indicate the same sort of object would find no one capable of learning his language. For example, instincts so-called not only have their vicissitudes but they have a multiple origin as seen in the example of birds cited already. Instincts undergo changes in their neural structure as well as in their later functioning. A primary unity undergoes defusion or differentiation in relation to the multiplicity of zones through which it finds an expression, and again undergoes fusion so that it becomes unrecognizable unless we give its parts different names. This is not a theoretical point: failure to appreciate this may lead to grave errors in therapeutic interpretation. Such premature interpretation, premature because of our continued ignorance, will again make us attach to the term a psychical fact to what is one of our own heuristic fictions. *And in this sense heuristic means it works for us or in the interest of our hypothesis.* Would it were that those who claimed to know the structure and dynamics of the infant psyche admitted that they speak in terms of hypothetical and not categorical and axiomatic knowledge!

That the infant with what Winnicott describes as soma-psyche has a species of implicit unity is logical enough: again, Coghill's work on the embryo shows that there is such unity and potentiality for behaviour. Let us for a moment consider what is the relationship between Id and Ego institutions, which imply so much in both paleo-Freudian and Kleinian dynamics.

At one time, and the picturesque myth language is not mine but that of the orthodox, the Id became differentiated under the influence of experience into an Ego vested in perceptual processes. "Where Id was, there Ego shall be" is a very useful working statement. But we have both institutions; we are told

that the Ego is in warfare against Id demands—a warfare which is unceasing and even aggravated by the early growth of a Super-ego, borrowing its energies from the Id and thus squeezing the Ego between an upper and nether millstone. The Ego does, however, play a large part in the life of adjustment and is at first purely perceptual. But our latest researches into perception (*vide* Hebb's *Organization of Behaviour*) show it to be replete with motor components—see also Adrian's electric enquiries into olfactory perception. Instinct and perception are wedded—the Ego or its earliest manifestations are fragmentary, by no means unpurposeful in a biological sense, but singularly unstructured in a psychological sense. Indeed, hardly is it possible to assume a capacity for true objectivity, let alone appreciation of objects—for at this stage sensory experience consists of little more than a multiplicity of signals for action. Perhaps the claims of early gestalten have been pitched too high, that James' blooming, buzzing confusion is perhaps not altogether a misguided description of early perceptual experience.

To assign, therefore, capacities to the infant in its first year without the instrument for their operation is to throw back adult analytic values to a phase where they dissolve into the darkest night.

Indeed, the long period of dependence of the human infant tends to extend the dark winter night, and because of the relative limitation of stimuli it is hard to believe in the highly structured phantasy life, which has been claimed to exist and can scarcely be substantiated. To me it is a welcome sign that in Winnicott's article on "Transitional Objects" he retreats, I think wisely, into the term "transitional phenomena", an admission of uncertainty as to what is really implied. He adds very wisely that more observations need to be made in this field and that it is a field in which many direct observations are possible which would give us data for a check-up system through which analytic findings could be usefully established. In fact, there are very clear and hopeful signs that this behaviouristic approach in the broad sense is being followed with encouraging results. I regard the work of Spitz, Goldfarb and Bowlby as signs of this pursuit on the part of those who could hardly be accused of antagonism to the basic principles of Freudian psychopathology. Here at least we see child behaviour in relation to primary figures being examined at first macroscopically, so that the fine adjustment, as it were, of analytic findings can be focussed upon demonstrable facts. I hold that it is important at this stage in our insight therapies to pause and look at accumulated facts so that we can see them as part of a procession of events whose course can be mapped out parallel with the observations made, say, in play studies with the very young, uncrystallized by such interpretations, which while they may influence behaviour in a curative direction, may only too easily arrest the natural autonomously directed processes in child behaviour by statements which in themselves create a pattern determined by our own doctrines. If we do not from time to time check up on our psychopathological fictions by observations, we may by purely deductive reasoning formulate elaborate doctrines of increasing complexity. The good craftsman gets excellent results from a minimum of tools: the amateur only too frequently feels in need of more and elaborate tools to gain the same end. How often do we notice how simple behaviour has been given recondite interpretations and how quickly the speculative heuristic concepts of the master are transformed into real things and real mechanisms because they are an aspect of them. No sooner had Freud thrown out the suggestion of a Death Instinct with a pseudo thermodynamic explanation than some analyst discovered them straightaway, elaborating a fundamental aggression process unsubstantiated except within the already

existing system of ideology. The merest tyro of psychiatry and the debutante in psychopathology discovers a population of bad and good objects in the youngest infant whose only language is a cry. The three institutions of Freud in some hands have become five and the Ego has been triplicated to meet not the facts of analytic discovery but the hunger for more and more complex mechanism. Fairbairn has himself warned himself as well as his readers against seeing this growing internal population as a return to demonology. (How excellent it would be if every young analyst were given a birthday gift of Occam's razor!) If mental concepts were cut down to a minimum we might have, it is true, fewer interpretations and more time for facts. A moratorium on interpretation might be usefully introduced.

There is no reason to doubt that the best line of approach to the understanding of mental growth is through process theory, or to use the current threadbare term, dynamic concepts; but we cannot have it both ways, that is to give a fixity to psychic institutions and at the same time to make them into moving parts of a mechanism. As Fairbairn says, internalized objects have a dynamic independence which cannot be ignored. What does that expression mean? Either they are objects with outlines, frontiers and meanings and, if so, then their dynamism lies outside them, or they are the fleeting moments in process which needs a different nomenclature altogether if we wish to free our language from melodrama. Poetic diction is fine for poetry and from its suggestiveness next steps can be made, but science cannot live on metaphor alone. It seems to me that psychopathology which roots itself in the child psyche must get away from mid-nineteenth century mechanics; the confusion of such mechanisms with psychic growth is out of step with the best in modern experimental psychology and functional neurology. These disciplines admittedly have their own fictions, but they are factually constellated and are rapidly shed with the advent of new facts which repeatedly call for new hypotheses where the old ones have not acquired an axiomatic authority.

So far I have belaboured you with the problems which arise from language and misplaced authority, the Idols of the Market place and the Idols of the Theatre; and I have tried to stress the fact that these preoccupations do not confine themselves to theoretical issues alone, for in my submission, as bad currency drives out good, so where there is bad theory there is bad practice, and where theory passes too easily over to practice without due circumspection we have the seeds of corruption. Nevertheless I can pass to consider a more practical issue which cannot thrive unless it arises from well-considered theory growing out from practice or concrete studies. Here indeed one can say are the Idols of the Cave, the realm of shadow concepts which men see and accept by too much privacy of vision. The now familiar term "the multidisciplinary approach" is a fairly modern attempt to correct the errors of prejudices of individual observation in subject matter which derives from a variety of sources. Now this multiple approach is not comparable to the employment of a variety of techniques as in general medicine where we use the special gifts of the biochemist, the microscopist, the radiologist. The investigation of the whole human being in his various aspects calls for study not of partial functions but of divisions of function as the methodologist sees it. In child psychiatry once upon a time the physician was able—or so he regarded himself—to deal with the whole child in the confines of his consulting room and this autocracy was born of the narrow view of child mental health seen by the paediatrician, who viewed behaviour as a function of disease or metabolism or viciousness. Now with the rapid growth of general psychology, the progress in the psychopathology of the family

in its social setting, the emancipation of psychiatry of childhood from paediatrics, the psychiatrist, the psychiatric social worker and the educational psychologist crouch for employment in every clinic; but although in the American model each contribute for the benefit of the psychiatrist's enlightenment, we are still being concerned with the dominance of one or other of the three. The fight of local authorities to possess and to structure clinics need not concern us now. I am concerned with the advantages and disadvantages of this not so holy Trinity examined in the light of the art of fact finding and the dangers of fictions which each discipline creates for itself as preliminary to shaping its hypotheses as to the part it plays in the disorder of a given child. It is a matter of both theoretical and practical interest to determine at what stage each worker is most useful. Moreover, it might be asked in reverse of this proposition what fallacies are introduced by separating functions which are in reality indivisible and which are only separable on pragmatic grounds or because, in common parlance, neither one nor the other of the team can be a jack of all trades.

There was a time—and not in the distant past—when a child analyst would take on the task of elucidating a child's disorder without any co-operation, let alone interference from the parents, guardians or school. They stated the problem, retired discreetly and left the stage to the analyst and his charge. I think there are a diminishing number of such autocrats; certainly the clinic renders this isolationism almost impossible. What fallacies are abolished and indeed what fallacies are introduced by the team approach? *Prima facie* there is economy in fact finding, but against this we are confronted by the attitude to facts which each specialist brings to the common task. The psychiatrist may come from mental hospital practice, perhaps with little or no training in paediatrics and with, let us concede, some general knowledge of psychopathology but with a Kraepelinian set of blue prints of mental disorder, not in terms of their ontogenesis but in terms of a very clear-cut phenomenology or ikonography. His concepts are fictions in so far as they are satisfying, easily handled tools for a diagnosis. For adult psychiatry they are valuable, economic and yield rules for reasonable prognostics. When leavened by the genetic, historic attitude engendered by a basic psychopathology, the diagnostic and prognostic accuracy is increased by the addition of a new dimension. For a long time this conjunction of the classical psychiatry with the undertones of mental development derived from psychopathology was sufficient for pragmatic purposes, until the discordant notes of two sometimes divergent views of each became more apparent. When the general psychologist's aid was solicited—and I am speaking of the early days—his or her contribution was that of psychological testing for I.Q. the specialist abilities, estimation of linguistic imperfections which were sometimes regarded as causes of emotional disorder in their own right. The dimension revealed and measured was treated as a unitary process—emotional or orectic factors were generalized and were revealed say as appearing in “scattered” test responses. The psychiatric social worker arrived on the scene with sometimes striking pictures of family life and neighbourhood qualities viewed in the light of social concepts. The fiction of the family as a unit, as a social product, as an economic instrument for survival, gave an interesting slant which might, and sometimes rightly so, modify the psychiatrist's conception of the processes he had seen or had inferred from his doctrines. In the case conference of the formal kind, the facts collected from the three main sources were brought together for the purpose of interchange and discussion. One frequently had to ask oneself are the facts collected by the several specialists logically comparable and, still more so, were the instruments for their collection and

description comparable. A collection of psychometric specialists could agree upon the interpretation of results from tests whose utility and accuracy as the base of accepted standards could be agreed upon. Fundamental axioms regarding "G" status of tests, and what special ability tests disclosed, could be widely accepted even admitting the hypothesis regarding "G" and so forth. Turning to the facts collected by the psychiatrist concerning history and alleged processes, it is obvious that in terms of quantification on the one hand and axioms of mental growth and dynamics, there is a world of difference between the two disciplines—while each may possess a high degree of internal consistency, they are two universes of discourse which overlap as regards *facts* of behaviour but may have few points of correspondence as far as concepts of mental mechanisms are concerned.

Moving over to the social psychiatric descriptions of family and social events, the convergence of psychiatry on social studies may be more obvious but again their concepts need not necessarily overlap for, as Durkheim expressed it, social facts are best explained by social facts; and even if we adopt the nomenclature and technique of Lewin that all members of a collective of mother, father and child (or children) possess group qualities, or better still properties of the life space they occupy, they are psychiatrically individuals. Lewin would, of course, have accepted the interplay of the internal life space of the individuals and the field properties which family life itself imposes. A psychoanalyst sympathetic to the field theory of Lewin would have reasonable grounds for accepting the nomenclature but might not be prepared to assimilate the emergent qualities of group existence which he would interpret as nothing more than an elaboration of social ties from the primary libidinal ties of the parent-child relationship. Furthermore, the educational psychologists also accepting this nomenclature might add that the school or the nursery life each has its essential qualities; that the child in these fields has to adopt the roles emerging from this field. Indeed the facts as collected are coloured by the hypotheses which each observer brings to his observations. In other words, as already argued, the fictions of each are presented as facts; and again these facts are moulded by the instruments of collecting. Some two years ago when the follow-up on results of therapy were considered at the Inter-Clinic Conference, it was suggested by Dr. Barbour and myself that an approximation to accuracy of assessment could only be arrived at by comparing the judgments of independent observers, the child, the parents, an independent psychologist, the teacher or other person with knowledge of the child. Even if they all agreed that the child was better, worse or stationary, their agreement could only come about by preliminary common agreement as to stable behaviour, adaptation, adjustment, or what you will, but we would still be in the dark as to the mechanism producing the change unless all the facts were disclosed to all the judges at simultaneous moments in the process from start to finish of the treatment whatever technique were adopted.

Fortunately within recent years conditions have changed in the direction of training of those who participate in team diagnosis and treatment. Psychiatrists have become more conversant with psychopathological concepts of mental growth, psychiatric social workers have shared this new orientation, and psychologists have emerged from the laboratory and lifted their eyes from statistical tables to take cognizance of emotional factors and to adopt a more receptive attitude to psychopathological claims. The convergence has been even sharper since so many members of a team have recognized the desirability of a training analysis to close in their personal scotomata and meet one another on a

common conceptual platform. This leavening has not only sharpened individual insights but has made team work easier. But there are certain patent disadvantages which cannot be ignored and which spring, I think, from the greater readiness to accept common fictions which have not been presented as hypotheses for confirmation by research. It seems to me to be a pity that with this convergence each department of specialism tends to blunt the edge of its own viewpoint. The psychiatrist of phenomenology loses some of his powers of detached observation, his sense of distance by plunging headlong into psychopathology, the social observer may neglect his or her social awareness because of the satisfactions and fascinations of depth psychology and the psychologist in his turn may lose that critical gift which comes from submitting all phenomena to tests and verifying procedures. In my submission much must be lost for the progress of our subject if the trained specialist abandons his specific skill which he should bring to the team meeting. Only in this way can we check up on one another's collected facts. In so doing we shall, and admittedly by soft degrees, confirm our hypotheses and so render diagnosis more reliable and our pursuit of treatment more and more free from the fictions which can be so satisfying, so restful and, in the long run, so misleading. And this, I think, is most clearly shown in our work upon the very young. How much do we really know of the early growth of infants from stark and laborious observations; or how much do we know about the common habits of mothers in their care of children and the habits of the fathers who in recent years have been left so much out of account.

We should, I believe, make slow but solid gains if we decide in our research projects to wed the fundamental concepts of psychopathology to observational techniques so that our hypotheses take the place of dogmatic fictions, and these hypotheses are confirmed by rigid checks. Comparative studies of different cultures will disclose much, for the claims of analysis cannot be accepted unless we study the variances in different social groups. Social anthropologists with the greatest sympathy for psychopathology have shown that instincts are not only inhibited in the aims according to different usages, but are much more plastic than we ever imagined. This will, I think, dissipate some of the rigid notions that we have been adumbrated about the mind of the infant. There is no intrinsic harm in having fictions as long as we pause to examine them before interpreting too freely the intentions of the infant whose destiny is in our hands. And lastly, for the sake of our growing science, too, we might well make fewer claims until such time as we have cleared the Augean stables of unwanted theories about realms which are still too dark for our instruments to penetrate.

HIBICON

A NEW ANTICONVULSANT

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INTRODUCTION

IN spite of the large increase in the number of anticonvulsant drugs in the three decades since the introduction of phenobarbitone, new remedies are constantly being sought. The present state of therapy of the epilepsies remains rather unsatisfactory. Drug therapy, which is still the most widely used form of treatment, is at best a maintenance treatment, i.e. the patient has to continue with it at least for many years to control the attacks. Even then a large number of sufferers continue to have seizures, often as frequently as once a month, which elude treatment. Surgery, which has found a wider application recently, is not radical either in many cases, and has to be followed up by medication over many years. The situation is further complicated by the fact that many anticonvulsant drugs, even when effective, produce unpleasant or dangerous side effects and have to be abandoned. One has also to consider the enormous psychological effects of the disease on the patient. The social stigma which epilepsy confers and the continual threat of an impending fit are often far more disabling than the actual seizures.

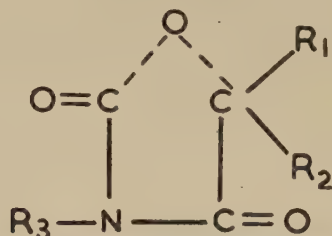
Lately three favourable clinical reports have appeared in American journals on a new anticonvulsant drug called "Hibicon" (Gotton *et al.*, 1951; Kaplan *et al.*, 1952; Hawkes, 1952). Lederle Laboratories Division, American Cyanamid Company have kindly put a quantity of Hibicon at our disposal for a therapeutic trial in this country. We are reporting our experiences with this drug on a group of forty patients suffering from various types of epilepsy.

PHARMACOLOGY

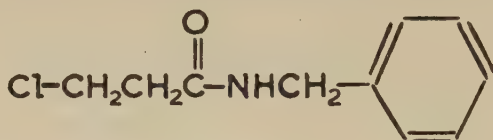
Lederle Laboratories Division, American Cyanamid Company had been experimenting with several compounds which contained a benzylamid residue, and which were found to have anticonvulsant properties when tested on rats. Kushmer *et al.*, (1951) from that Laboratory have reported on the preparation of 23 new benzylamides which they tested for anticonvulsant activity. One of them "Hibicon", was found to be clinically active in the treatment of grand mal epilepsy. The chemical formula is N-benzyl- β -chloropropionamide. It is a white crystalline solid with a molecular weight of 197.6 and a melting point of 90 to 92°C. It has a low solubility. It raises the electrical threshold in laboratory

animals and is also effective in the metrazol test, but less so than tridione. It was tested for acute and chronic toxicity in various animals and was found to have a wide margin of safety. The peak of the action is reached two hours after administration and there is little accumulation.

Hibicon is particularly interesting chemically in that it does not contain the group which all other anticonvulsants hitherto used have in common (Toman *et al.*, 1948) (see Fig. 1).



This group appears in most anticonvulsant drugs (from Toman *et al.*, 1948).



Hibicon.

The capsules are rather large and have a dark brown colour. Later on Hibicon was supplied in small cachets of orange colour. This we felt was an improvement.

MATERIAL

The case material consisted of two groups of patients. At first one of us (J.H.) administered the drug to twenty-one out-patients attending the out-patient department of the Maudsley Hospital. They were all patients treated at Dr. Denis Hill's Clinic. There were twelve men and six women, their ages ranging from 18 to 56. The remaining three patients were children aged 6, 8 and 8½ years.

The diagnoses could be loosely grouped into three categories:

- (1) Idiopathic epilepsy with major seizures: ten adults and one child.
- (2) Psychomotor epilepsy with demonstrable epileptogenic foci in the temporal lobes, confirmed by electroencephalogram: three adults and one child.
- (3) Focal epileptogenic areas in other parts of the cortex and taking clinical forms other than psychomotor seizures: five adults and one child.

One patient in Category 2 had Jacksonian attacks in addition to the psychomotor seizures. The suspected lesions responsible for the seizures in the patients of group 2 and 3 varied in their pathology. They included head injuries, encephalitis, lesions very likely due to birth injuries, etc. Of the children one dated his attacks from a cerebral thrombosis, the other had a history of whooping cough, with seizures beginning one week after the onset of the illness and persisting up to the present time.

The mode of selection of the patients for treatment with Hibicon was not uniform. Five patients were recent admissions to the clinic and had never been treated before; thirteen patients had been attending for some time but had not responded satisfactorily to other drugs, and three were included in the trial because, although their seizures had been fairly well controlled by other medi-

cation, they had shown side effects from these drugs. One of these patients had developed ataxia while on phenytoin, and two had hypertrophy of their gums due to prolonged treatment with hydantoinates.

The patients attended the clinic at regular intervals of one week to one month, as the case required. Before treatment began they had all been fully investigated and a diagnosis had been made. They all had several EEG's done.

The second group consisted entirely of in-patients of St. Francis Hospital, Haywards Heath, a mental hospital. All of these patients had very intractable seizures and some had marked personality disorders in addition, which made hospitalization necessary. They were all chronic patients and had been in hospital from two to fifteen years. They were chosen for treatment with Hibicon because they persisted in having at least one seizure per week in spite of treatment with other anticonvulsant drugs. As can be seen, they constituted a most difficult group of patients to treat and presented a formidable test for a therapeutic trial. There were ten women and nine men. Their ages ranged from 23 to 60 years of age. Their diagnoses fall into three categories: eleven patients had "idiopathic" epilepsy, seven had temporal lobe foci presenting with atypical attacks, and one patient had multiple cortical foci due to arteriosclerosis. Two of the temporal lobe foci were caused by head injuries, the others were of unknown pathology. The high proportion of temporal lobe epilepsies is in accordance with the findings of Liddell (1953) who analysed all epileptic patients in a mental hospital and found temporal lobe lesions in over half of them. Almost all patients had personality disorders in addition to intractable seizures. In the case of fourteen of these patients these disorders would necessitate hospitalization even if there were no fits.

The two groups are so different that we shall report them separately.

DOSAGE AND METHOD

Most workers agree that a dose of one to two grams of Hibicon three to four times a day is effective in most adults, whereas in children 0.25 to 0.5 g. three to four times per day suffices. Kaplan (1952) was using smaller doses, but got equal if not better results. In his series the number of fits was reduced by more than 50 per cent. in just over half the patients. In a further 20 per cent. there was a reduction in the number of fits by 25 to 50 per cent. Hawkes (1952) could achieve "adequate control" in 66 per cent. of his group.

In the present series the adult patients were given 0.5 g. three times per day as the initial dose irrespective of whether they were already on anticonvulsant treatment or not. After one week the previous medication was very gradually reduced, withdrawing not more of the daily dose than 0.2 g. epanutin per week and other drugs were withdrawn in similar proportions. When the number of fits increased during this withdrawal period the daily dose of Hibicon was increased by 0.5 g. every week. The Hibicon dose continued to be increased at the same rate after all other drugs had been withdrawn until either all fits were suppressed or a maximum of 1.5 g. three times per day was reached. If fits still persisted in spite of the ceiling dosage, other drugs such as phenobarbitone or epanutin were added in the usual doses.

As far as the Maudsley Hospital group of patients is concerned this scheme was modified in that the maximum dosage was kept at 1 g. of Hibicon three times per day. This caution was adopted because the patients were out-patients and could therefore not be observed as closely as the second group at St. Francis Hospital. Seven patients took 1 g. three times per day, nine patients took 0.5 g. five times per day, and two patients took 1 g. twice per day;

eight patients had to have phenobarbitone 1 to 2 gr. daily in addition, and six of those had phenytoin 0.1 g. two to three times as well before the maximum benefit was obtained. Three children had 0.5 g. Hibicon three times per day, and one of them had phenytoin 0.05 g. twice daily in addition.

Of the St. Francis group of patients, fifteen had to have 1.5 g. three times per day and eleven of those had phenobarbitone $\frac{1}{2}$ to 1 gr. per day in addition; seven of these patients had epanutin 0.1 g. two to three times per day as well. Two patients had 1 g. of Hibicon four times per day, one patient had 1 g. three times per day and one had only 1 g. twice daily.

Several of the patients objected to the treatment because of the large size and dark colour of the capsules. It will also be noted that the number of capsules which make up the maximum dose is nine, and if other tablets have to be taken in addition the number of preparations which a patient has to take is rather formidable. In view of our remarks about the psychological aspects of the treatment of epilepsy this was a serious handicap.

RESULTS

The results can perhaps be most aptly presented according to the response of the different type of seizures. In the Maudsley Hospital group the results were as follows:

The number of major seizures decreased in four patients, showed no change in four patients and increased in three patients. The psychomotor attacks responded very well. All four patients who suffered from that type of seizure improved. The number of Jacksonian attacks decreased in four patients and increased in three. Several of the patients reported that they felt generally better since treatment with Hibicon had started. It is perhaps noteworthy that all the children did well; not only was the number of attacks reduced; but they were reported by the parents to be more alert, and when the treatment had to be brought to an end these patients were very distressed.

The St. Francis Hospital group did not do so well as the Maudsley Hospital group. It must be borne in mind that this group consisted of particularly difficult cases. The number of major seizures decreased in six patients, showed no change in four, and increased in one. The temporal lobe seizures decreased in three patients, remained unchanged in two, and increased in two patients. The patient with cerebral arteriosclerosis who had atypical seizures improved. Six patients of those included in the improved group were completely free of seizures for several months. As far as the behaviour difficulties are concerned they improved markedly in at least one patient. But in most cases no change for the better was noted.

Table I shows the results taking both the Maudsley Hospital and St. Francis Hospital group together. This table illustrates that over half of the patients showed some degree of improvement. The table does not indicate such results as improvement in well-being and behaviour, which, although not always present, were nevertheless very striking in a small number of patients.

TABLE I

					Improved	No Change	Worse
Major seizures	..	..	..	..	10	8	4
Psychomotor seizures	..	..	..	..	7	2	2
Atypical seizures—Jacksonian	..	..	..	..	5*	—	3
Total	..	..	..	..	22	10	9

* This figure includes the patient who had Jacksonian attacks in addition to psychomotor seizures.

SIDE EFFECTS OF THE TREATMENT

The animal experiments showed a very low degree of toxicity and a wide margin of safety (Kaplan, 1952). The clinicians were struck by the relative absence of untoward effects of the treatment. Kaplan (1952) found no unpleasant side effects in his patients. The hypnotic effect, so troublesome with many other anticonvulsants, is absent with Hibicon. Hawkes (1952) found dizziness and slight gastrointestinal distress in some patients which he attributed to the treatment. These did not seem dangerous and did not persist.

These reports are borne out by our own experience. While under treatment with Hibicon all the patients had periodic blood counts and urine examinations carried out. Three patients showed a transitory leucopenia which disappeared even when treatment was continued. This reaction has been observed previously in relation to other drugs such as thiouracil (Young, 1949), tridione (Hoenig, 1951) and others. Young (1949), explains that this reaction is quite distinct from agranulocytosis, is transitory and not serious. Twelve patients complained of transitory dizziness, and one developed a tendency to fall to the right which lasted a few days without showing any other clinical signs referable to the nervous system. It is worth noting that the patients who had hypertrophy of the gums due to epanutin improved in that respect while on Hibicon. The only two serious complications which we encountered were (a) four patients lost weight while on the treatment, in the range from 8 to 12 pounds and (b) three patients developed status epilepticus in spite of the very gradual withdrawal of the previous medication. It is not very clear why this came about. It is not likely to have been merely a direct result of the withdrawal of previous anticonvulsant treatment, as it occurred in one patient several months after this withdrawal was completed. The patients were treated with Sodium Gardenal and recovered. Neither the loss of weight nor status epilepticus had been observed by previous workers.

DISCUSSION AND CONCLUSIONS

Hibicon therapy has produced better results in the out-patient group treated at the Maudsley Hospital than in the in-patient group at St. Francis Hospital. This is to be expected in view of the type of case treated at St. Francis, i.e. the sort of patient who is so severely afflicted that he has to be confined to hospital for many years. Furthermore, out of a whole group of mental hospital patients suffering from epilepsy, only those were chosen who had not responded satisfactorily to other types of medication. Considering this fact, we came to the conclusion that Hibicon does at least as well as hydantoinates. As is usual when different types of anticonvulsant drugs are compared, some patients who have not done well on one, do better on the other; or else some seem to get slightly worse when changed over to the new medication. This trend is also apparent in the present trial. We find that over half of the patients showed some improvement, not only in regard to the number of seizures, but in a few cases also in regard to general well-being and behaviour. But on the other hand, a quarter of the patients seemed to get worse. These results bear out previous reports by Kaplan (1952) who reports in 50 per cent. of the patients marked improvement and in 25 per cent. slight improvement or no change, and Hawkes (1952) who finds 39 per cent. of his patients improved, and 28 per cent. worse, and finally Gotton *et al.* (1951) who achieved in 17·5 per cent. excellent control; in 30·5 per cent. some improvement and in 52 per cent. no satisfactory control. As most of these trials only refer to small numbers of patients, the slight fluctuations in results are probably not significant. Hawkes (1952) was treating

a control group, adequately matched, with hydantoinates. The results in his two groups were fairly equal.

As regards the response of the different types of fit to the treatment, our figures would indicate that psychomotor attacks associated with focal lesions in the temporal lobe do particularly well. Our figures, however, are too small to allow definite conclusions in this respect. In view of the fact that this type of epilepsy has proved to be the most intractable so far to non-surgical methods of treatment, this finding is certainly worth further investigation. Should the psychomotor seizures be proved to respond at least as well as the major seizures the result would be very encouraging. Previous workers have also reported favourable results with psychomotor seizures, but their groups did not contain many patients suffering from that type of attack. Kaplan (1952) had one patient in whom the number of seizures were reduced by over 50 per cent., and Hawkes (1952) states that psychomotor attacks showed some response although not as good as major seizures. As regards petit mal seizures Hawkes (1952) reports that they do not seem to be affected by Hibicon. None of the patients in our group had petit mal type of attack, and the present trial cannot add anything with regard to the response of this type of epilepsy to Hibicon.

The most remarkable finding is the absence of toxic or unpleasant side effects. In so far as any did appear, namely giddiness and mild nausea, they were transitory and did not prove an obstacle to treatment. The three cases of status epilepticus are of course extremely serious. None of the previous workers has reported status epilepticus occurring during treatment. In fact we are not clear about the aetiology of the status. As we pointed out above, it is unlikely that it was precipitated by too rapid a withdrawal of previous medication. It is possible, although we have no evidence to offer in support of this view, that the entirely different chemical structure of Hibicon from other anticonvulsants may invoke a change of electro-physiological balance in the central nervous system, leading to a transitory instability during the change over which, in turn, increases the liability to serial fits. It would seem that, until we know more about it, the utmost caution is indicated when patients are changed to treatment with Hibicon.

As regards the loss of weight observed in some patients the connection between this and Hibicon is even more difficult to understand. It may easily have been coincidental. Some of the patients who showed the loss in weight did generally poorly, but two improved in other respects.

Another difficulty is the fact that in order to achieve an adequate dosage a large number of capsules has to be taken by the patient. This should not be taken lightly in view of the importance of the psychological aspects of epilepsy and its treatment. In the case of Hibicon this difficulty was particularly noticeable as the capsules are of a large size and an unpleasant dark brown colour. These are factors which are probably quite easy to remedy.

We would finally conclude that Hibicon does not seem particularly superior to hydantoinates. It does produce better results in some cases but not in all. It is certainly worth adding to the list of anticonvulsants to be tried in resistant cases. Furthermore, the absence of side-effects makes it a safer drug than most other anticonvulsants, and in patients where hydantoinates have produced such side effects as acne or hypertrophy of the gums, Hibicon will prove a useful alternative treatment, possibly for long periods or perhaps only as a temporary standby until the toxic effects of the previous medication have subsided.

SUMMARY

Forty patients suffering from various types of epilepsy were treated for six months with Hibicon. The results are on the whole at least as good as with hydantoinates. Psychomotor

attacks in particular show an encouraging response. The drug is particularly innocuous and produced only very minor and transitory side effects. Hibicon is a valuable addition to the anticonvulsant armamentarium.

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THE PROBLEM OF AGNOSIA IN THE LIGHT OF A CASE OF PURE WORD DEAFNESS

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INTRODUCTION

ALTHOUGH pure word deafness (p.w.d.) is a well-defined clinical picture it usually occurs as part of a more complex syndrome. Almost invariably there is some degree of aphasia and as a rule other auditory disturbances, such as imperception of specific sounds including musical tones, also occur. These associated symptoms tend to diminish or even disappear in time while the deafness for word sounds usually persists in its initial intensity. In the case we describe most of the associated symptoms, especially the aphasia, soon abated leaving an almost pure word deafness. Subsequently this too improved slowly and because of the partial recovery we were able to obtain data which are rarely available in these cases.

Pure word deafness can be regarded as an agnosia for word sounds. Recognition of agnosia as a specific disorder has not been altogether unopposed, the point at issue being the evaluation, particularly in visual agnosia, of peripheral factors, and the position has been critically reviewed by Critchley (*The Functions of the Parietal Lobes*, 1954). In pure word deafness the peripheral complications are less frequent and when present their effect is easier to assess. Nevertheless the difficulty in distinguishing between peripheral damage and cortical (agnosic) disorder remains and it has always been noted that the word-deaf person behaves as if he were deaf. One of the objects of this paper is to re-examine this point and through it to discuss the problem of agnosia in general.

CASE REPORT

The patient, R.C., is a sheep farmer, aged 45, married with two children. His history is irrelevant prior to the onset of his present illness, the early symptoms of which have been obtained from his wife. On the morning of 15 September, 1953 she found that she could not understand his speech, which she described as an indistinct mumbling, and at the same time he appeared to be completely deaf. He paid no attention when spoken to, did not seem to hear the wireless and did not notice noises such as a door banging. Over the next few days his speech improved rapidly. At first he uttered only single words but he was soon able to form a sentence, though he frequently used words wrongly, especially when he wanted to say something definite or important. Within a fortnight, however, his powers of speech returned almost to normal and he only made occasional slips. On the first day of his illness he picked up his paper but did not carry on reading and his wife did not know whether he could read or not. Within a few days he was reading papers and magazines but told his wife that he easily lost the thread of the story. For a few days after the onset of the illness he was unable to count his sheep. Later he could do so but had to write down the numbers in tens and twenties. Within a week he was able to restart his farm work and carried it out as efficiently as before. He made no complaint of physical illness.

In contrast to his rapid improvement in all other respects, the patient's "deafness" remained unchanged. He was quite unable to understand the spoken word and his wife had to carry on a conversation with him in writing.

His wife states that prior to the onset of the illness he was fond of music and had a good ear. After the onset he occasionally whistled but never a recognizable tune. He was right-handed but used his left hand more than most right-handed people. He had been accustomed to making up his own accounts and writing his own business letters.

The patient was first seen as an out-patient on 23 October, 1953, five weeks after the onset of his illness. He was found to be word deaf and was admitted to the Crichton a few days later

for fuller investigation. He was under observation in hospital from the end of September to the middle of December, 1953. After his discharge he was seen as an out-patient at weekly intervals for the first few months and then at longer intervals until the present. The picture he presented was that of pure word deafness, the deafness for word sounds being for a considerable period complete. Minor symptoms were occasional slips in his speech, some writing difficulties, and difficulties in musical expression and rhythm. Neurological examination revealed slight enlargement of the left pupil but was otherwise negative. His blood pressure was 114/90. Wassermann was negative in blood and cerebrospinal fluid and this was also normal in other respects. The history and symptomatology thus suggested a cerebral vascular lesion.

DISCUSSION OF THE SYMPTOMATOLOGY

Two phases can be distinguished in the illness of our patient: an acute transitory phase in which massive aphasic disturbances were combined with an imperception of auditory stimuli in general and a more persistent second phase of severe word deafness when his speech had recovered and auditory perception of sounds other than those of speech had returned to normal. The clinical picture in the second phase was one of pure word deafness which as in similar cases in the literature was the residuum of an initially diffuse aphasia. The information we have of the first phase of the illness is from the patient himself and his wife. During the second phase the patient was for eighteen months under observation. The discussion refers mainly to the investigations carried out in this second phase.

Audiometric testing was carried out eight weeks after the onset of the illness when the patient's word deafness was still almost complete. He stated at this time that his hearing was perfect; he could hear everything, even a leaf falling, but he could not hear the "human voice". The testing showed a normal air and bone conduction in the right ear and a moderate mixed deafness in the left ear. These findings were unaltered on re-testing eight months later when the word deafness had considerably improved.

The perception of word sounds altered very little during the first months of observation; he was almost completely word deaf and communication had to be carried out in writing. Such persistence of word deafness has been observed in most of the cases of this type, and self-descriptions of the defect obtained from the patients are fairly uniform. Such patients say that speech sounds like a foreign language. They speak of a kind of murmur or humming noise. Similar descriptions were given by our patient and some of his other remarks are of interest. For instance he said "It is like a great noise all the time. Speech goes on and on. There is no stop. It sounds far away. You think you can catch it and it fades away. I can't get near enough. It is like a wall between, like a gramophone, boom, boom, jumbled together like foreign folks speaking in the distance. You feel it should be louder but when anyone shouts it is still more confusing." On other occasions it appeared to him that people were speaking too loudly, as if they were shouting. He therefore seemed to experience word sounds as distant and as an undifferentiated mass of sounds without structure or rhythm.

About twelve weeks after the start of the illness some improvement in word perception was observed and the number of words he perceived correctly gradually increased. His score with more familiar words and phrases was better than with more unusual ones. He is, however at the time of this report, that is after eighteen months of observation, still unable to carry on a sustained conversation and it is frequently necessary to resort to writing. In conversation, as he says himself, he guesses the content of a sentence from a few words he has picked up, but he never guesses the meaning of a particular word which he has incompletely perceived. The setting of the speech is a factor of considerable importance in his perception of word sounds; he has least difficulty when he is conversing directly with the person, but when he listens to people talking to each

other he is not able to follow a conversation and can only pick up an occasional word. He can follow conversation more easily when the person talks quietly, but when someone speaks "loudly or quickly the words just run together, two or three words run into each other". When listening to the wireless or when he converses while some noise is going on he is unable to pick up anything. It is of interest that at an auction sale he reports that he grasps what the auctioneer says at a distance better than when he is too close. Under less favourable conditions the word sounds are submerged into the background stimuli and his threshold for word sound perception is greatly increased.

There has been, however, a complete recovery of perception in certain respects. At a fairly early stage he was able to *distinguish the voices* of different people familiar to him. This seems to bear out one of his own remarks when he stated he heard the words as if separated by a wall. A normal person is able to distinguish voices but not the words through a wall. Somewhat later he stated that the English language no longer sounded foreign to him and he was able to distinguish between the various idioms. He could say whether someone spoke to him in the accent of his home county, or from any other part of the country, or with a foreigner's accent.

The voice in which the language is spoken is a musical quality of speech and this quality may be as A. Pick (1896) has shown the last residuum of a word deafness. In our case it was the first to recover. The musical factor may have aided our patient to identify his own language and idioms, but it also indicated that some differentiation in speech sounds had taken place, his speech was no longer merely a jumble of un-characteristic sounds. He was at this time able to pick up an occasional word but he said he could identify his own language and idioms without actually comprehending individual words. There was at this phase a certain overall familiarity with a succession of word sounds as distinct from the familiarity character of particular words which may precede the identification of words during recovery from sensory aphasia.

A particular point of interest was the *experience* he had while *speaking himself*. One frequently finds that aphasics are unaware of their mistakes and they may also have a feeling of strangeness both to other people's speech and to their own speech. Henneberg (1906) reported a case of pure word deafness who stated that he perceived his own speech unclearly or not at all. Our patient was questioned on this point on numerous occasions. His description was straight-forward and consistent, and the following are some of the remarks he made: "When I am speaking it sounds similar to what I hear when other people speak. It is indistinct. I do not hear it properly. My mind knows what to say. I know exactly what I want to say but I don't know whether it is right or wrong. If I could hear my voice properly I could think it was right. I don't know whether folk are hearing what I am saying. I know I am speaking but I can't hear the words right, not the actual words, I can hear the voice."

Our patient's statements refer to two different processes: firstly, to the sensory experience of his own voice and this seems to be identical to what he hears when other people speak; secondly, he refers to the experience he has during the process of speaking. He knows, he says, that he is speaking but he is not aware of his own words. In contrast, a deaf person, although unable to hear his own words, is fully aware of what he says and is in no doubt whether he uses the right or the wrong word. We will consider this phenomenon later when we discuss the mechanism of pure word deafness.

Repetition is the only objective way in which one can determine how the spoken word is being perceived. The validity of this test, however, is limited

in our type of case. It has to be remembered that the patient is not only unable to perceive the spoken word but that the entire act of perception has altered; the verbal sounds are indistinct, the auditory impression is fleeting and elusive and it is therefore difficult for him to give an exact replica of his auditory impression. Furthermore, as he is aware that verbal sounds are presented to him at repetition tests, he will have the tendency to reproduce speech-like sounds whatever his actual auditory experience may be. The following are characteristic examples from these tests during the early part of his observation in hospital. The word or sound spoken by the examiner is in brackets.

(u) "Ho". (p) "Cup". (l) "a". (Sugar) "Shlop". (Sense) "Seback". (s) "It". (d) "Back". (Tremendous) "Amsell". (Tip) "Anti". (bl) "Bit on". (Collaboration) "Setter". (Picture) "Ento". (Lesson) "Lastrom". (God Save the King) "As in a mix". (Good Morning) "Become". (There are clouds in the sky) "Are sore oror". (1, 2, 3, 4, 5) "Horses". (1-5) "When it has been nefrore". (1, 2, 3, 4, 5) Correct answer.

He was able to repeat vowels correctly, otherwise there was only an occasional similarity between presentation and repetition. Later, correct repetition became slightly more frequent. Some aspects of the alteration in his perception of verbal sounds are well-illustrated by these tests. There was little congruity between the actual sound composition and the patient's perception. The exception regarding the vowels can be explained by their particular character; they do not represent sounds specific for language. There was some indication that the experience of the span of time of a verbal stimulus was inaccurate. Long words often appeared to be short and *vice versa*. The large number of jargon-like reproductions was striking, a reaction previously recorded by Schuster and Taterka (1926) in their case of word deafness. The normal tendency to substitute word sounds indistinctly perceived by words of language was thus absent. This points to a fixation to the sound itself. In other words the patient was stimulus bound, and this was apparently an impediment to further elaboration. This factor was also evident when in his reproduction he had missed the correct composition of the word by one sound element and yet was unable to make the slight correction necessary for producing the correct word. This last reaction demonstrates the same all-or-nothing rule which we also noted in his perception of word sounds in conversational speech.

There was some progress in these tests during the later period of observation. His repetitions became more similar in sound to the word presented and a few words could now be repeated correctly in each session. His progress on these tests, however, lagged behind the progress he had made in the comprehension of conversational speech. With the latter he was able to guess the rest when he had picked up one or two words from the conversation. There was also some improvement in so far as he often finally produced the correct word at repeated presentation. On such occasions the correct word emerged suddenly without being preceded by gradual approximation to the word sound.

At the beginning of our period of observation the patient still had some difficulties in *verbal expression*; he made occasional slips in conversation, and in the naming of objects, but these mistakes later became more and more sporadic. He was never aware of such mistakes. Judging by conversation, naming, completion tests, definitions, naming of synonyms and antonyms, his speech resources were perhaps initially slightly below his premorbid level, for instance, he increased his scores on the Terman-Merrill Vocabulary Tests from 26 to 30 out of 45, the latter score being adequate for his intellectual and educational level. His reading was throughout fluent and without mistakes but

in the first week or two it often took him a considerable time before he grasped the content fully.

The picture of our patient so far shows the characteristic features of a pure word deafness; there was almost a complete deafness for verbal sounds without any appreciable difficulty in internal language.

There were, however, *difficulties in writing*, which though they gradually improved, were still present at the time of this report. Although he was not a very practised writer, prior to his illness he wrote letters quite adequately. While under observation he made spelling mistakes on dictation, numerous at first and more occasional later. He had difficulty in giving written descriptions of pictures, his work or his farm, descriptions which he could give orally in detail and without hesitation. When writing he was very slow and used a kind of telegram style. Though he knew the words he wanted to write, he had difficulty in spelling them out and therefore restricted his expression in writing to the utmost. His shortened style could be regarded as a stress symptom arising from the spelling difficulties and comparable with the telegram style of speech in certain motor aphasiae. ("Sprachnot" Isserlin.)

The *spelling difficulties* are not so easy to explain, contrasting as they do with the words freely and correctly spoken. The spelling defect could be regarded as the residuum of a disturbance of the inner language, but why spelling and writing should remain the only signs of such a disturbance requires explanation. The patient was, at a particular session, usually able to write down numerous names of objects correctly and without difficulty but at a particular word he became hesitant, uncertain and failed. Here are some of the mistakes he made: "Spetale" for spectacles, "Hankhesch" for handkerchief. "Citer" for cigarette, "Bottler" for blotting paper, "Pincatre" for picture. For bicycle he wrote "Bicl": when checking it up he said "There is something in between 'c' and 'l', but I cannot find out what it is."

These mistakes have to be considered in relation to his speech. When he still had difficulty in writing he had no difficulty in speech, and he could say the word correctly which he was unable to write. Occasionally when asked to write a particular word he seemed to be at a complete loss. He did not know how to start or what to write. On these occasions he said the word in question again and again as if attempting to get hold of it but was unable to say either the initial or end sound of the particular word or the succession of sounds. The word in question could be quite simple and its spelling phonetic. It seems that we have here the same phenomenon which we previously found with the self-spoken word; he could say the word but the word so spoken did not present itself in its sound composition. He apparently had no difficulty in writing as long as he could rely on his recollection of the written symbol, but he became confused when he had to resort to the recall of word sounds by means of speech.

Apart from our patient's word deafness only *rhythm* and *musical sense* were more persistently disturbed. Such disturbances have been frequently reported in cases of pure word deafness. His experience of the spoken word which, as he said, sounded as "going on and on without stopping" suggested a disturbance in rhythmic sense. To test this, Morse code was signalled by tapping on the table and the patient had to reproduce the signal. At first he was hardly ever correct, failing in even the simplest test, and his rhythm was always faulty. Later there was a gradual improvement, but he still makes some mistakes at the time of this report. The following tests were carried out to ascertain his musical sense. He was asked to identify popular tunes played on the gramophone, to accompany by humming or whistling a popular tune played to him,

and finally, he was asked to sing, whistle or hum a popular tune. He was able to recognize the majority of the tunes though it usually took a considerable time before he could do so. When he had, however, to reproduce tunes his performance was very poor. He was often unable to find the correct melody and even when he started with the right tune he easily lost it. He had the same difficulty with the rhythm of the tune. His musical defect improved gradually and after six months returned to normal.

The question may be asked why disturbances in music and rhythm are so often combined with pure word deafness and are often more persistent than the disturbance in perception of other auditory data. The greater vulnerability of speech sounds, rhythm, and music may be related to their relatively greater complexity, but there is another common factor in our case which deserves consideration. Rhythm, music and perception of word sounds require a registration of successive auditory data as distinct units. There was evidence that the time span of particular verbal sounds was only vaguely experienced by our patient and it seemed that preceding sound elements were already extinguished when succeeding stimuli arrived. Such disturbances would obviously affect in particular the perception of rhythm where registration of time intervals is essential.

In cases of pure word deafness in which musical disturbance has been noticed (Lipmann and Storch, 1902; Bonvicini, 1905; Stertz, 1912; Klein, 1927; Reinhold, 1950; Ziegler, 1952), the disturbance seems to be mainly a receptive difficulty in accordance with the receptive defect of language. In our case, musical expression was much more involved than musical perception. It will be remembered that our patient was unaware of the word sounds spoken by him, and a similar defect may have accounted for his difficulty in musical expression. One would expect such an unawareness and consequent loss of inner control to affect the expression of musical tunes much more than verbal expression.

The information we received from his wife suggests that he behaved at the beginning of the illness like a deaf person, there being no reaction to any auditory stimulus. The patient himself insisted when referring to this period that he did not hear anything, everything was "quiet" and when he was confronted with a person, he did not know whether this person spoke or not unless he watched his lips. Such general lack of response to auditory stimuli has been observed in various types of word deafness in the initial stages. It has been suggested that it might be due to an attention defect; but as has been pointed out in other cases (Stengel, 1940) such patients do not necessarily show any lack of attention to auditory stimuli in interviews or when tested. Although difficult to explain there is a corresponding reaction in the visual sphere. In the initial phases of visual agnosia the patients complain of blindness and impress as being blind. The "blindness" in visual agnosia later becomes restricted to special visual functions in the same way as in our case the "deafness" becomes limited to the sounds of speech. This initial deafness of the patients is probably closely connected with disturbances in perception and identification of *noises*. A number of cases are reported in which the patients were unable, although hearing noises, to identify their characteristics and this disturbance has in some cases been as persistent as the word deafness. Our patient had apparently no difficulty in identifying noises after the initial phase had passed. When we tested him there was no defect. Not only could he recognize promptly characteristic noises presented singly but he could also distinguish two or three such noises when presented simultaneously.

Finally there was at the beginning of his illness a transient disturbance in *numbers*. From the rather vague description of the disturbance obtained no definite conclusions can be drawn as to its character. It is not unlikely that it has some connection with the aphasic disorder which was fairly marked at this time. When we tested him after admission, no defect as to numbers or calculations could be discovered.

The patient restarted his work on the farm a week after his illness had begun and since then has managed the farm as efficiently as before. His intellectual performance when estimated by non-verbal tests two months after the start of his illness showed no sign of deterioration on digit symbols or on the Rorschach test but his scores on Raven's Matrices and Koh's Blocks were slightly lower than on re-testing six weeks later when he seemed to have returned approximately to his normal level. In these tests there was initially a fairly wide scatter. He might solve difficult patterns correctly and do poorly on very easy ones and he had some difficulty in altering his approach once he had adopted a particular procedure.

DISCUSSION OF THE MECHANISM OF THE DISORDER

It has been pointed out that our patient's word deafness cannot be due to a disturbance in auditory conduction. His hearing was not only satisfactory audiometrically but he had no difficulty in recognizing characteristic noises and tunes. Nor could his word deafness be an aphasic disorder, as no appreciable disturbance in language could be found at the time when the word deafness was still complete. Since he was unable to identify and recognize word sounds the disturbance belongs by definition to the agnosias. All the indications were that the agnosia was of purely perceptive nature; his auditory experience of word sounds had profoundly changed and not only was he unable to identify or comprehend word sounds, but their quality had altered; they had, for our patient, lost their specific speech character.

Some of the phenomena which illustrate this alteration in perception will now be discussed in more detail. One of the significant phenomena refers to the patient's statement that he is unaware of what he is saying. He knows what he wants to say and has no difficulty in selecting and expressing the correct word but when he turns the word into sound he cannot say whether he has used the right or wrong word. He is not aware of the word he is actually using. The patient naturally relates this disturbance to his difficulty in hearing, but, as is well known, it is not necessary to hear the words in order to realize what one is saying. The words may be drowned by noise but there is no uncertainty about them. Nor is a deaf person in any doubt whether he uses the right or wrong word. Under certain conditions the auditory control may even be a disadvantage, stutterers will often speak quite fluently when their voice is drowned by a rattle.

More important than the auditory control is the control of the self spoken word by inner language mechanisms. There are aphasics who feel that their own speech is strange and many others who are unaware of the mistakes they are making. This can be explained by the loss of word concepts. Because of this loss the patient is unable to identify words and the word spoken may appear strange or mistakes may not be realized. The problem in our case is, however, different. Our patient has no loss of word concepts, speech is well prepared and he has no difficulty in expressing himself. It is in our case not an unawareness of a defect but a loss of normal experience and reaction, the absence of which is realized and strongly felt by him. The word whenever phonetically formulated or turned into sound does not leave any trace and cannot be registered. Some

inner response to the word sounds, a kind of resonance, seems to be missing.

Another characteristic feature is the unselectiveness of his perception and the clinging to the sound when word sounds are presented. This was well demonstrated in repetition tests at a time when some organization of word sounds had already taken place. His reproduction of word sounds was at this period usually a jargon-like conglomeration of sounds, but when, as sometimes happened, his reproduction approximated in sound to the word presented, he rigidly adhered to this faulty approximation. He neither replaced it by the correct word nor did his reproduction suggest any meaning to him. The normal tendency to complete the word, incompletely perceived, was absent, and he appeared to be fixed to the sound. This reaction is of particular interest considering that his language was well preserved.

Normally when language has developed perception of word sounds is directed towards registration of the word concept and only a small proportion of sounds is necessary to convey the meaning and is actually perceived. Our patient, in contrast, absorbs all or too many sensory impressions. He collects and accepts them indiscriminately. This refers not only to sounds of speech but to accessory sounds which accompany speech. Speech appeared to him at the beginning of his illness as a continuous humming noise and even now he is unable to pick up the spoken word when listening to the wireless and has great difficulty in comprehension if more than one person participates in the conversation. One could compare our patient's reaction to that of a deaf person who starts to use an amplifier. He will at first have greater difficulties than before because accessory sounds, which are amplified simultaneously with speech sounds, now interfere with perception. In order to perceive the acoustic "word gestalt" he has to learn to disregard these accessory sounds. Some mechanism has to be established by which the confusing sound elements are eliminated, and a similarly acquired mechanism has apparently become defective in our patient. Such a mechanism, centrally controlled, may have a suppressor or analyser action so that sounds are selectively perceived and perception can to a certain degree be detached from sound.

There is finally the general qualitative change in our patient's experience of word sounds. They may be experienced too loudly and thus appear too near, or they may fade away and appear to be distant. A long word or sentence may appear short or *vice versa* and the patient is thus unable to estimate the exposure time of a particular word or sequence of words. The location of the source of word sounds in space is indefinite and the span of time is only vaguely experienced; perception of word sounds is therefore without any precise spacial or temporal order. The same word sounds are at various sessions or on successive occasions experienced quite differently and there is no constancy in our patient's word perception. No trace seems to be left of word sounds that are just received, their impression is fleeting and they are prematurely extinguished. A succession of word sounds is perceived as an uninterrupted and uniform continuum of sounds; there is no differentiation as to sound character and the rhythmic qualities of speech are not experienced.

The process of our patient's word perception is as pointed out, arrested at a sensory level; this arrest shows various signs characteristic of a disorganization in Gestalt formation. It has been claimed (Goldstein *et al.*, 1918; Goldstein, 1926) that the inability to build up Gestalten is due to a general factor arising from a lowering of intellectual functions and that this inability is accordingly always more or less generalized. This is not the case in our patient, for there was only a minor and transitory defect in general intellectual functions, and the

disorder was for most of the illness confined to the perception of word sounds. The disorder was thus strictly circumscribed.

Though our patient was unable to experience word sounds as characteristic wholes, this does not necessarily mean that there was primarily a disturbance in the presumptive capacity for forming Gestalten. Some of the phenomena observed rather suggest a disturbance of more elementary mechanisms, at a relatively low level of sensory organization. Thus the phenomena we described as an absence of inner response and failure to eliminate accessory sounds would indicate that the defect is at a stage preliminary and preparatory to structuralization. This may also be true for some of the other phenomena such as the disorganization of word sounds in time and place, the lack of constancy and the premature extinction.

We would therefore suggest the following interpretation of our patient's word deafness. There may be a disturbance of a centrally regulated process or apparatus which has the function of fixing the word sound material, separating this material from the acoustic background, desensitizing it, and adjusting it to a systemic order which forms the basis of cerebral organization. The severe disturbance of word sound perception and its arrest at an amorphous sensory level, which is otherwise difficult to explain, would be understandable when such apparatus is out of action. In general such a process could serve the purpose of co-ordinating a variety of heterogenous functions into a homogenous system and transforming sensory material into mental data.

SUMMARY

A forty-five year old man showed after a probable vascular lesion of the brain a marked aphasic disorder and absence of response to auditory stimuli. After a short period lasting only a few days, the aphasic disturbance had almost completely disappeared; the picture which followed was that of a pure word deafness associated with disturbance in rhythm, musical expression and some disturbance in writing. On audiometric testing, carried out six weeks after the start of the illness, the air and bone conduction of the left ear was normal and there was a moderate mixed deafness in the right ear. At this period the word deafness was still almost complete. The verbal sounds were experienced as an undifferentiated continuous humming noise without any rhythm. Subsequently a gradual limited improvement in the word sound perception occurred, but there was still a considerable defect after 18 months of observation. The sequence in which perception of various qualities of speech recovered was followed up, and a number of phenomena associated with the word deafness were studied.

Some of these phenomena considered to be significant for the mechanism of the disorder have been discussed in detail.

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AN INVESTIGATION INTO CHILDREN IN AN ATTEMPT TO DIFFERENTIATE BETWEEN MENTAL DEFECT AND DEAFNESS

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THROUGH the generosity of the South West Metropolitan Regional Hospital Board a research unit for the study of apparently deaf children with defective speech was set up in Belmont Hospital in March, 1953. The primary object of the unit is to attempt to assess by methods which will be discussed later whether children who have acquired no speech are in fact only deaf or whether they are mentally defective, emotionally disturbed, or are suffering from these or other conditions. It is an undoubted fact that some children who have never spoken and who are therefore inaccessible and who may be asocial or antisocial in their behaviour are diagnosed as being mentally defective and spend their lives in mental defective institutions. It has however already been shown in our unit that a number of these children when under observation for a period of time prove to be deaf and probably educable. If facilities were available to continue their education under specialized conditions they could no doubt make useful citizens within their limitations. Before discussing the problems associated with these children in more detail it might be as well to describe the personnel and layout of the unit.

The unit, which is self contained in a special block of the hospital, is capable of admitting up to seven children at a time for investigation. The children sleep in a dormitory and in addition have a large room used as playroom, dining and schoolroom. There are also a playground and large shed attached where they have swings and a sandpit and the usual recreational facilities found in a small school for young children. The day-to-day administration of the unit and the health of the children are left to a qualified nurse, while in addition there are three children's supervisors who look after their general welfare such as feeding, washing, toilet habits and recreations. One of these supervisors has a nursery nurse's training while the remaining two are unqualified apart from experience with children. There is also a full-time Teacher of the Deaf. Psychiatric, electrophysiological, psychological, and ear, nose and throat investigations are carried out on each child. In some instances where the diagnosis tended towards that of mental defect rather than deafness and it was thought that there might be an organic cause, air-replacement studies

have been done at Hurstwood Park Hospital. After the children have been in the unit for some time case conferences are held where all members of the staff are present and an attempt is made to assess the child's disability and its possibilities in the educational field.

MATERIAL

Since the establishment in March, 1953 some 22 children have been in the unit for varying periods of time as well as two who were known to be mentally defective. In all cases they were children who could not be assessed either mentally or audiometrically in one or even two sessions as out-patients, largely owing to masking of the underlying condition by emotional upset. The majority of these children were between 4 and 8 years of age while one was over 12. Nineteen of these twenty-two children did not speak in any form, and superficially all of them appeared to be deaf. Six of the children were hyperactive, one usually quite violent. Eight were withdrawn, two very markedly so. Two spoke with a marked speech defect, and one with a slight speech defect. Many of the children had neurotic symptoms, such as enuresis, faecal incontinence, screaming attacks and tantrums. Neurotic reactions were found to be common among the deaf children in the unit not only as a result of their deafness and consequent frustration but also as a result of their difficult homes. Fourteen of the children had parents who frequently quarrelled and some of the mothers had left home. Other mothers had no time for the deaf child who was more or less an outcast and rejected by the family, or the child was such a drag on the mother that she herself became anxious and neurotic. A number of children had spent long periods in hospital for operations such as hare-lip or illnesses such as tuberculous meningitis and were unable to adjust themselves to the home environment on their discharge. Two of the patients had otitis media following measles, five had had tuberculous meningitis and two had suffered from fits in infancy or childhood. In four cases there was a family history of deafness. It is interesting to note how many of these children had congenital abnormalities. These were present in eleven of the twenty-two children admitted and included hare-lip and cleft palate, two cases; eye defects such as squint and coloboma, six cases; double hernia, one case; undescended testicle, one case; valgus deformity, one case; kernicterus and erythroblastosis foetalis, one case; and bronchial fistula, one case. One child had multiple congenital defects.

METHODS

Most of the children on admission were emotionally disturbed and gave no indication of their true potentialities. This difficulty had to be at least partially overcome before the child's disability could be assessed, and the environment was planned with this in mind. If there was some response to the environment, then teaching could be started in an attempt to determine the child's educability. The reaction of the child to the environment and the teaching play a large part in determining whether the child is backward due to deafness or mental defect.

Environment. Each child is encouraged to behave as normally as possible and the staff encourage and help the child to make the most of its abilities. There are fixed times for meals, toilet and teaching, but apart from these times there is a large amount of freedom. Problems of behaviour and discipline are dealt with according to the individual needs of the child rather than to any fixed standard of behaviour. Outings on a bus or to the parks are weekly treats that help to give the children a normal life and in time the majority gain confidence and their behaviour becomes more natural. When the confidence and co-operation of the child have been gained, tests of hearing and of educational ability can begin.

Educational ability. The child's educational ability is tested on two levels of activity, general and specific. Owing to the nature of the child, tests must follow the interests of the child and a great variety of techniques and apparatus is required. On the general level raw materials such as sand, water, clay and bricks are provided and the child's play with them is observed for signs of ability to use them with increasing skill, to play imaginatively and to work out ideas. Play situations are made such as washing, cooking and cleaning and repeated from time to time to test the child's ability to learn from experience and to relate what he sees done by the adults around him to his own activity. On a specific level, testing is based firstly on the perception of the relation of similarity and difference and secondly on the power and desire to imitate. The first is fundamental to an understanding of the environment and is the essential root of reading skill and of comprehension of number. Ability to acquire this perception is tested by graduated play apparatus. These range from coloured spills which have to be sorted and different shapes which have to be put into their right hole, to words and sentences of different shape which have to be put to the appropriate picture or followed by the appropriate action and, also, to different sized groups of objects which have to be placed by their appropriate number symbol. The power and desire to imitate is obviously dependent to a great extent on awareness of and good relationship with the adults in the environment and is essential to the development of writing and speech. The child's ability to imitate is tested in games in which he must copy the adults' actions before being given what he wants. He may be provided with paint, chalk or crayons and helped and encouraged to use them, or encouraged to imitate speech sounds. Observation is made on how far in these circumstances the child is willing and able to copy the adults around him.

Hearing. The ability to assess hearing must depend upon some positive and objective response to an auditory stimulus. Very few of these children respond to ordinary audiometric routines and therefore other ways have to be found. These depend upon the ingenuity of the people who are making daily contact with the children, bearing in mind the principles of audiometry. Usually, from day-to-day observations, some idea of hearing ability is formed. At some time or other, mostly when the child is eager to do something such as eat or play with a particular toy, his attention is focussed and he will respond to a spoken order; in this way some of the children were found to have normal hearing. In the case of those without normal hearing the play method has to be established over many weeks. The well known Ewing method of response to "go" or some other voiced sound is practised until sooner or later a level of hearing is established. Some of the children were never able to be trained to do this. At the same time other more formal methods were tried. See page 125.

Mental ability. Assessment of mental ability was by means of the Merrill Palmer Pre-School Scale and the Drever-Collins Battery. These were selected because the material is interesting enough for this type of child to play with and also because both tests may be used without the need for speech on the part of the examiner or examinee. Because of their difficulties very few of the children would respond immediately, but in time all except a very few did respond enough for an assessment to be made.

Electrophysiological methods. Various physiological methods for examination and measurement of cerebral auditory function such as electroencephalography, psychogalvanometry (P.G.R.) and various forms of audiometry have been studied in an attempt to assess quickly the nature of the defect in these children. It is unfortunate that the very nature of the defect and the attendant

TABLE 1

Age	Sex	Family History	Congenital Defect*	Birth Injury	Relevant Illness†	Environ- mental Stress‡	Speech		EEG Abnor- mality	EEG K Complex	P.G.R. Follow- ing Sound Stimulus	Hearing	Mental Ability§	Educa- bility	Length of Stay
							Dumb	Jargon or Limited							
R.B.	6	M	+	-	+	-	+	+	+	...	...	?partial	no co-operation	-	2/12
M.B.	8	M	+	-	+	+	+	+	-	...	...	normal	I.Q. 105	+	14/12
J.B.	3	F	-	-	+	+	+	+	-	+	...	partial	below level MP scale	?train- able	4/12 Improved socially.
C.B.	5	M	-	-	-	-	+	+	-	...	+	normal	below level MP scale	-	6/12
J.C.	7	M	-	-	+	+	+	+	+	...	-	normal	no co-operation	-	5/12
N.C.	6	M	+	-	+	+		+	-	+	-	partial	M.A. 47/12	+	5/12
S.C.	10	M	-	?	?	+	+	+	...	...	...	none	I.Q. 75	+	2/52 Discharged school for deaf. Good progress.
R.D.	7	M	+	-	-	-	+	+	-	-	-	none	M.A. about 4 years	-	12/12
B.D.	3	M	-	-	+	+	+	+	-	+	...	?normal	no co-operation	+	5/12 Still in residence.
D.E.	8	M	-	-	-	+	+	+	-	...	+	normal	M.A. 2 11/12	-	5/12 Learnt tones easily.
J.F.	9	M	+	-	+	+	+	+	...	...	-	none	?due to muscular inco-ordination	+	6/12 Recently described. At school for back-ward deaf.
J.H.	5	M	-	-	-	+	+	+	?	...	...	?normal	no co-operation	-	2/12
W.H.	13	M	+	-	-	+	+	+	+	...	...	none	no co-operation	?	6/12 Discharged school for deaf but not kept.
K.H.	2½	F	-	?	+	+	+	+	-	...	...	normal	below level MP scale	?train- able	4/12
T.J.	5	M	-	-	-	-	+	+	-	+	+	partial	M.A. 4	+	17/12 Still in residence. Starting to talk.
D.P.	4½	M	+	-	+	+	+	+	-	-	...	none	no co-operation	?	3/12 Improving socially. Still in residence.
L.P.	5	F	-	-	+	-	+	+	...	...	...	?normal	no co-operation	-	2/12 Mental test affected by poor sight.
A.R.	4	M	-	-	-	+	+	+	-	...	...	partial	I.Q. 60	+	10/12 Minor epileptic attacks since discharge.
R.W.	10	M	+	-	-	+		+	+	+	...	partial	varied results	+	7/12 Still in residence.
C.W.	8	M	multiple +	-	+	+		+	?	-	...	none	M.A. 4 11/12	?	12/12
P.W.	5	F	+	-	-	-	+	+	-	+	...	normal	M.A. 4 7/12	+	5/12
W.W.	5	F	+	-	-	+	+	+	-	+	...	normal	M.A. 4 7/12	+	5/12

* See text p. 122.

† See text p. 122.

‡ Bad home situation or institution, +, - Mental Age refers to Merrill Palmer test. Minimal level about 14 years. I.Q. measured using Drever-Collins Battery of tests for deaf children.

§ Mental Age refers to Merrill Palmer test. Minimal level about 14 years. I.Q. measured using Drever-Collins Battery of tests for deaf children.

behaviour has made the tests difficult and sometimes impossible to do even after repeated attempts. The following methods and their value when applied to this type of child have been studied:

1. Electroencephalogram: (a) awake for exclusion of cases with a recognized pathology; (b) asleep for study of response to sound.
2. Psychogalvanic reflex in response to auditory stimuli.
3. Audiometry: (a) speech audiometry using standard recordings; (b) pure tone audiometry using peep-show.

(1a) EEG awake. In only a few instances was it possible to obtain EEG's sufficiently free from movement artefact to make interpretation easy, and most tests had to be confined to one anterior and posterior and to one or two transverse recordings. Over-breathing tests and recordings with the eyes closed were not practical. It was thus not possible to make observations on EEG changes such as blocking of the alpha rhythm in response to sound.

(1b) EEG asleep. In the early stages of sleep, stimuli such as a prick or sound, if sufficiently startling, may produce a brief, large amplitude group of waves with a characteristic form—the K complex—maximum at or near the vertex. Some workers have thought that it is possible by this means to obtain an audiogram. It is however not at all clear that the appearance of a K complex indicates that a sound stimulus has arrived at the auditory cortex. The specific response of the auditory cortex occurs much sooner after the sound stimulus than does the K complex and is confined to that area. It is very small in size and can rarely be detected without special methods.

It has been suggested that the K complex in man may correspond to the response that can be evoked in animals by stimulation of the brain-stem reticular formation. The response in animals can also be produced by an auditory stimulus and it seems that this response may occur independent of the activity in the specific projection to the primary auditory cortex. The occurrence of a K complex following an auditory stimulus shows that the auditory pathway up to the brain stem is functioning, but it does not necessarily follow that if the subject has been awake he would have heard a sound. Apart from the uncertainty of the meaning of the K complex in relation to actual sensation there is from the point of view of audiometry the undoubted fact that clicks are far more reliable than pure tones in producing a complex. This fact has been mentioned by other workers and it has been verified here.

One further and perhaps the greatest problem has been to obtain the light sleep in which the K complex is seen. It is important however to try and obtain an EEG during sleep not only for the study of the K complex but because epileptic tendencies and certain cerebral pathological conditions may be revealed. The study of the K complex will certainly indicate whether or not the peripheral auditory pathway is functioning and there is here a quick method of determining something of the hearing of a child.

(2) Psychogalvanic reflex (P.G.R.). An auditory stimulus will probably not produce a P.G.R. unless the sound has an unexpected or startling quality. Preliminary results by Ackner and Pampiglione at the Maudsley Hospital have shown that as soon as a state of light sleep is obtained a stimulus will no longer evoke changes in the skin resistance. It is perhaps then permissible to assume that in order to obtain a P.G.R. or change in skin resistance the sound must be perceived. If a P.G.R. is obtained following a sound stimulus then it would appear that both the peripheral and central auditory pathways are functioning. A test on these lines should indicate whether or not a child has any hearing, but

the results have been disappointing in that on some occasions, even when a child was known from observations to have a considerable amount of hearing, no P.G.R. was obtained with the loudest sounds available. Stimuli such as a prick or patting on the head did produce a response except in one case and there was therefore good evidence that the efferent side of the reflex mechanism was unimpaired. Where there was a response to loud sounds results differed from day to day. This variable response to sound was a common observation in the unit. In order to obtain audiograms by this method several workers have used a slight electric shock following the sound stimulus in order to condition the subject and thus obtain threshold values of hearing. It was thought that this method would probably be upsetting to children to whom a peaceful, stable environment was essential, and it has therefore not been used. If a P.G.R. is obtained following a sound stimulus then there can be no major interruption to the auditory pathway at any level. If a P.G.R. is not obtained it does not mean that the subject is necessarily deaf, but that the sound may have lost its startling or unexpected quality. The absence of a P.G.R. where there is known to be hearing usually appears to have a psychological explanation, but in one or two of the children the absence seemed almost pathological. It is interesting to note here that in a series of 50 defective children studied, a P.G.R. was obtained in response to sound stimuli in the majority of cases.

(3a) Audiometry. Speech or music using standard recordings. A method was evolved for determining the level of hearing of speech or music in the children who could obviously hear something, but who either could not be encouraged to co-operate in pure tone audiometry or who were unable to do so. Two types of tape recording were made, either of music to which the child seemed to respond or, if the child seemed to understand speech, a recording of commands such as "show me the house", "show me the car", the objects being in front of the child at the time of the test. The output from the tape recorder was put through the audiometer to the earphones so that the level at which it was being played could be determined. Judgment of the response to music depended chiefly on facial expression and the results were not very satisfactory. The children who could do the other test enjoyed it and obviously had great satisfaction in picking up the various objects and finding the right one. The children who did this test could not be said to be greatly defective although they were certainly backward.

(3b) Audiometry. Pure tone using the peep-show. For the younger children who did not know objects the peep-show on the same lines as Denmark's modification of Dr. Hallpike's original idea has been built. Three of the children under six have been examined so far. Two learnt the idea of the test fairly rapidly and audiograms were obtained after three or four visits. One difficulty encountered is that the child's attention wanders when the sounds are at threshold and nearby levels and the hearing may be better than is indicated. This method too is obviously not without its pitfalls.

RESULTS

The 22 children admitted did not form a clear-cut clinical group, although in twos or threes they might have been said to resemble each other. There were no constant factors present in the history, such as rubella in the mother during pregnancy, injury or cyanosis at birth, or history of middle-ear disease. A definite history of rubella during pregnancy was obtained in only one case and hyperemesis gravidarum in another. At present the numbers investigated are too few to warrant any supposition as to the importance of aetiological

factors apart perhaps from those who had meningitis, but when more children are seen it is possible that clear-cut groups may emerge which may show some correlation with aetiology, family history or congenital abnormalities. Nine of the eleven children with congenital abnormalities were finally considered to be either totally or partially deaf. Whether this tends to show that in these cases the deafness was congenital it is impossible to say at the present time, as the opportunities for carrying out post-mortem examination on such children are almost negligible. Only one child in the group had a clearly abnormal EEG, the type of abnormality being similar to that seen associated with epilepsy. There was no constant finding in the EEG's of the other children. No gross focal abnormality or asymmetry of the rhythms was observed except in the one instance, but in a few cases there was more slow activity of 4-5 c/s. and medium amplitude in the temporo-occipital areas than might have been expected for a child of that particular age. This type of abnormality has not been seen sufficiently often for any significance to be attached to it at the moment. The appearance of slow activity in a child's EEG does not necessarily indicate some underlying cortical pathology. Most of the EEG's were thought to be within normal limits.

As has already been stated many of the children have neurotic symptoms. The majority of these children quickly responded to the environment of the unit where they were accepted as members of a group, were given affection and so felt secure. In the course of a few weeks their tantrums and enuresis tended to disappear and they began to play with the other children instead of being isolated and asocial units as they were on admission. Where the methods used to gain confidence and co-operation were not enough the child remained withdrawn. With these children practical tests of hearing and educational ability were found to be impossible. Fourteen of the twenty-two children showed improvement in co-operation and awareness over periods ranging from three to twelve months and five of them did not. The two children who were known to be mentally defective and not deaf and who were being used for controls among the problem group also did not improve in co-operation and awareness. Their reactions to training, teaching and daily routine were almost negligible and bad habits such as destructiveness, dirtiness and inability to feed themselves were much more difficult to eradicate, while it was much more difficult to inculcate new habits. Three of the children were not in the unit long enough for it to be possible to come to any conclusion concerning their reaction to the environment. Of the sixteen children who had bad home conditions ten improved and four did not. Four of the fourteen children who showed improvement were judged to be sufficiently stable to be able to take their place in a normal environment. The behaviour of the others in spite of their improvement would still cause difficulty in a school or at home and it seems that there is need for longer treatment and observation in these cases.

DISCUSSION

It is known that some children presenting a picture similar to those in this unit, of lack of speech and difficult behaviour, have eventually improved sufficiently for them to take their place alongside normal children and have made worthwhile progress. Various problems then arise. How may the child be fully assessed? When and how do they first change from being too difficult for normal methods of education to becoming able to take their place in a normal school? What kind of environment is needed to make the child amenable to a normal learning situation in the shortest possible time?

It is quite clear that the majority of children need a period of stay in the unit before any assessment of their disability can be made. Electrophysiological methods can help to give some idea of whether the auditory pathway is functioning. However, even if it were shown conclusively that a stimulus was arriving at the auditory cortex, there is no means of telling how that sound is being interpreted except by observation. Apart from the necessity of giving the child confidence and improving its social behaviour, it was found that many of the children had to be taught that sound had a meaning before any assessment of their hearing could be made. In the same way a child had to be encouraged to learn so that his ability to do so could be judged. In order to do this it is necessary for the children to have almost individual supervision and tuition, and in large classes they would undoubtedly be unable to make the progress which they do in this unit. One great difficulty is to place the children who have been found to be educable along normal lines. It is possible that much could be accomplished where home tuition is available. A house purchased through the generosity of the Nuffield Provincial Hospitals Trust and the Regional Board run on home lines and in charge of a foster mother will be opened soon for those children in whom emotional upset appears to be the greatest factor causing their disability. It is hoped that these children will respond favourably to the home environment and so make investigation of their condition possible. According to their ability they could finally take their place in a normal deaf school or could be trained to do some sort of work at which they could earn a living. One point to be noted is that the earlier these children can be assessed and taught the better their chances of responding to teaching. Those children who have had little or no education before the age of ten and upwards are unlikely in most cases to benefit by training. We do not yet know when these children change from a picture primarily of defectiveness to that of the deaf, backward adolescent found in mental defective homes. Observation over several years of a number of such children may help to solve this problem, and also to give some idea of the most suitable environment for them.

From this brief general survey it will be seen that these children present a most difficult problem, but certainly not one which can be dismissed. There is yet no means of making a satisfactory diagnosis, but it is already felt that much can be done over a period of time to assess their condition and educability and that where there is any doubt about a child it is entitled to a period of observation in a unit similar to this.

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PROGNOSIS IN PSYCHIATRIC DISORDERS OF THE ELDERLY

AN ATTEMPT TO DEFINE INDICATORS OF EARLY DEATH AND EARLY RECOVERY

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PROGNOSIS, the prediction of the outcome of an illness, has long been recognized as a necessary skill of a physician. Hippocrates (translated Chadwick and Mann, 1950) said:

"It seems highly desirable that a physician should pay much attention to prognosis. If he is able to tell his patients when he visits them not only about their past and present symptoms, but also to tell them what is going to happen, as well as to fill in the details they have omitted, he will increase his reputation as a medical practitioner . . . It is impossible to cure all patients: that would be an achievement surpassing in difficulty even the forecasting of future developments . . . By realizing and announcing beforehand which patients were going to die he would absolve himself from any blame."

In addition to the reasons given by our distinguished forebear we now also require to read into the future so that we can make the best use of the limited facilities available for the sick. This is particularly true for elderly psychiatric patients for whom treatment facilities are still very inadequate. It has been suggested (Cook, Dax and Maclay, 1952) that mentally ill elderly people should by preference be admitted to short-stay units attached to general hospitals for the assessment of prognosis and probable response to treatment. They suggested that a 3-4-months stay might be necessary. Experience in a diagnostic out-patient clinic (Norris and Post, 1954) led one of us (F.P.) to believe that it should be possible to classify patients according to the best method of dealing with them in a shorter time even than the six weeks recommended by the B.M.A. Report (1947). The present study was designed to test this belief. Our hopes were only partly fulfilled, but a *post hoc* analysis of our original data, in conjunction with the known results of the follow-up of cases, has suggested that with more knowledge of the factors influencing prognosis over a short term, much more accurate forecasts could have been achieved. The second half of this paper is devoted to a discussion of these factors. A preliminary report was given at the Third International Congress of Gerontology (Kay *et al.*, 1954).

METHOD

During a six-months period, when D.W.K.K. worked as a medical officer in an observation ward for mental patients, F.P. and D.W.K.K. examined and assessed all patients over 60 years of age *within ten days of admission*. The progress

of 229 patients so obtained was followed by correspondence with medical superintendents or relatives for just over one year after discharge from the observation unit. Twelve cases were excluded, because of the failure to follow them up (eight cases), or because the patients died or were transferred before an assessment could be made (four cases). It was hoped that from this investigation: (1) we could compare our predictions with the observed outcome and so determine whether or not our criteria of prognosis were valid; (2) we could re-examine our clinical records, in detail, in relation to the known outcome and decide what factors are likely to be of most general use for prognosis. Our concern was to predict for each patient both survival and social recovery, and the data on which our predictions were based are given below.

RECORDS EMPLOYED IN THE INVESTIGATION

For every patient a card was made out on which were recorded the following data:

- (1) *Name, sex and age.*
- (2) *Civil Status.* Single, married, separated or widowed.
- (3) *Domestic Status.* Living alone, in an institution, with spouse, with friends or relatives.
- (4) *Social Contacts.* Divided into two categories—socially isolated, used regardless of domestic status, in those cases where patient had not been in regular and friendly contact with at least one person or group; all others were counted as socially integrated.
- (5) *Physical Health.* Full health, senile decrepitude, presence of definite signs of physical disorder, state of the central nervous system, blood pressure and heart.
- (6) *Mental State.* Previous psychiatric history, and presence of the following signs or symptoms:
 - (a) functional, i.e. neurotic, affective, paranoid;
 - (b) psycho-organic, i.e. mild dementia, definite dementia, positive psycho-organic symptoms.

DEFINITION OF TERMS USED TO DESCRIBE MENTAL STATE

1. *Functional*

Neurotic: included obsessional, phobic and hysterical symptoms.

Affective: anxious and agitated states were classified with depressive and manic pictures under this head.

Paranoid: this label was used rather than "schizophrenic" because persecutory thought content was common in association with organic mental syndromes and with functional illnesses which could not be readily classified as either affective or schizophrenic on the basis of our brief assessment.

2. *Psycho-organic*

Two basic types of organic mental picture were distinguished:

(a) *Negative symptoms:* classified either as "mildly demented" where intellectual status appeared to be not fully preserved, or as "definitely demented" where from history and examination there was clear evidence of a permanent impairment of cognitive and/or other personality functions.

(b) *Positive psycho-organic symptoms:* acutely disturbed behaviour, often with transient delusional and hallucinatory experiences, when it occurred in a setting of diminished awareness.

It is possible for both psycho-organic types to be present at the same time, e.g. an episode of senile delirium in the course of senile dementia; more rarely positive psycho-organic symptoms may be present at the same time as functional symptoms, e.g. a confusional episode in a psychosis with depressive features complicated by toxic or cerebrovascular factors.

Data recorded in this manner epitomise on a single card the main clinical and environmental features of each patient. To give two examples: Mr. A. is a widower of 68 living with members of his family where he remains well integrated; he has a physical illness, left hemiplegia, with a B.P. of 190/110 but without circulatory failure; there is evidence of definite dementia having occurred, and of some positive psycho-organic symptoms, visual hallucinations at night. Patient B. is 73, single, living alone and without any social contacts; without there being any physical signs of illness she shows some general decrepitude, a B.P. of 140/105, and some evidence of mild intellectual impairment in the presence of paranoid symptoms and absence of affective disturbance. In this way we obtain a clinical description of a multidimensional type which conveys much more than labelling patient A as suffering from a cerebro-arteriosclerotic confusional state, or patient B from a senile paranoid state. Our aim had been to collect data during a brief observation period and frequently in the absence of an adequate account of the development of the illness, the two clinical assessors did not feel justified in allocating every case to a definite nosological entity. They did attempt, however, to place each patient into one of three main diagnostic categories, taking into account signs and symptoms culled from the available history as well as from the observations of the nursing and medical staff. In the absence of clinical phenomena of the kind seen in the organic mental reaction type, the patient was allocated to the Functional Group; when there were no neurotic, affective or paranoid symptoms the patient was called Purely Organic. Where there were present both organic and functional psychiatric symptoms, the case was classed as belonging to an intermediate Mixed Organic-Functional group. We were not concerned with investigating whether patients in this intermediate group, with both psycho-organic and functional mental symptoms, were in a transitional stage of an illness which might have begun as a functional psychosis and developed into a terminal state of organic dementia, nor did we attempt to assess whether the functional symptoms, e.g. depressive affect, were different in quality from those found in a purely "functional" illness at this stage. Our impression was that the great majority of the patients in this mixed group were suffering from one of the organic psychoses of old age with functional admixtures resulting from their personality structure. But it will be shown that taking account of the presence of these functional admixtures is of value in assessing individual prognosis. Table I shows the main characteristics of our group of patients.

Finally, the two clinical investigators by agreement committed themselves to predictions with regard to survival and duration of hospital stay before social recovery (discharge from psychiatric in-patient care). Death or social recovery were forecast to happen within less than 1 month; 1-3 months; 4-12 months; not within one year. Before making these predictions the investigators had agreed on a number of hypothetical prognostic factors, and on the way in which they thought these criteria might influence the duration of life and/or stay in the hospital. As it will presently be shown that the predictions were successful to a limited extent only, it is unnecessary to enumerate in detail the prognostic indicators used. A clean bill of health without any positive psycho-organic symptoms, except perhaps in the form of a brief confusional episode on

TABLE I

Composition of the Sample Used in this Study, Showing the Frequency of its Main Clinical Characteristics, and their Relation to Outcome

	Diagnostic and Age Groups						All Diagnoses and Ages		
	Functional Group 60-69 years and Over		Mixed Functional/Organic 60-69 years and Over		Organic Group 60-69 years and Over				
Total Sample	..	Persons ..	..	..	36	43 (7)	27	80 (31)	217 (39)
Sex Distribution	..	Males ..	..	..	9	19	8	32	75
		Females ..	..	..	27	24	19	48	142
Outcome	..	Dying within 12 months	..	..	6	11	15	46	82
		In-patient at end of 12 months	..	..	10	17	4	29	66
		Recovery within 12 months	..	..	20	15	8	5	69
Clinical Features (Note: these are not mutually ex- clusive so the totals in this group do not add up to those shown in row 1)	..	With C.N.S. disease	..	..	11	15	16	39	82
		With positive psycho-organic symptoms	..	..	12	15	22	54	103
		With definite dementia	..	..	18	23	17	63	121
		With mild dementia	..	..	15	17	3	4	39
		With previous attacks	..	..	14	10	4	5	52
		With social isolation	..	..	6	13	6	25	54

Figures in brackets show numbers of patients aged 80 years or more.

admission, was regarded as indicating survival for at least one year; on the other hand, death was thought likely at an early date in the presence of a serious physical illness, especially when associated with persistent positive psycho-organic symptoms. Assuming that men had a higher mortality than women, predictions in males tended to be less favourable than those for women in a comparable group. Social recovery, i.e. discharge from mental in-patient care, was thought unlikely in all cases where early death had been predicted, and also where people had been admitted from lonely living conditions or had been leading a socially isolated existence. Recovery was also thought unlikely in the presence of definite dementia and of paranoid symptoms (unless these had occurred in socially integrated persons with little or no intellectual deterioration, or in the setting of an acute affective illness). Early recovery was predicted on the basis of a history of previous short stays in psychiatric units, most commonly on account of confusional episodes accompanying reversible physical illnesses (including minor cerebrovascular accidents), or of brief affective reactions in unstable personalities. Between these extremes, recovery within 1-3 months or 4-12 months was predicted according to the estimated proportion of favourable and unfavourable clinical and social factors present.

COMPARISON OF PREDICTED OUTCOME WITH OBSERVED OUTCOME

Our expectations that attempts at predicting which patients would die in less than one month, in 1-3 months, 4-12 months, or would live at least 12 months, might prove over-ambitious, were realized. Predictive failures were strikingly obvious in our attempts at forecasting which patients would die and which would survive during the first as against the second and third months after admission to the observation unit. Even when limiting our predictions to deaths occurring during the whole of the first three months, we were correct in only 30 of 58 cases; similarly, for the 4-12-months period only 10 of 24 deaths were correctly predicted. In the less ambitious project of merely predicting who is likely to die within a year of admission and who will probably survive at least 12 months, the results showed that we had been too pessimistic in our forecasts both of survival and of social recovery. Instead of the 97 deaths forecast, only 82 actually took place; and there were 135 patients who survived instead of 120 predicted. Of the 97 expected to die, 33 in fact survived; and of 120 expected to survive, only 18 did not. In all, 97 persons were predicted to die within a year and in 64 cases (66 per cent.) our forecast was correct, whereas 120 persons were expected to live at least 12 months and 102 (85 per cent.) of these fulfilled our expectations. In over three-quarters of the cases, therefore, we correctly predicted the state of the patient at the end of one year.

For social recovery, as with deaths, our predictions were unsuccessful, although not to the same extent, in determining which patients would make a rapid social recovery. Of the 44 persons who recovered within the first three months half were predicted correctly, and of the 25 recoveries occurring during the period 4-12 months just under half were expected. Restricting our aim to the forecast of recovery within 12 months, we correctly predicted 49 (i.e. 71 per cent.) of the 69 patients who did recover in that period, and 135 (i.e. 91 per cent.) of the 148 patients who did not recover in that time. In all, in respect of social recovery, we were right in 85 per cent. of our predictions when we tried only to distinguish recoveries taking place within one year.

To sum up, we failed mainly in predicting the patients who either died or recovered within the first few months of admission. Our success lay in picking out correctly 85 per cent. of the patients who survived the first year after

admission and 71 per cent. of those who made a social recovery during that period.

Anticipating briefly the results of an analysis of our data in the second part of this paper, our failures to predict correctly the outcome of illnesses during the first few months appear to have arisen from a number of faulty evaluations. Though aware of its importance, we underestimated the high mortality of males, especially those with physical disorders; we did not fully realize how infrequent social recovery would be after the age of 70, and survival after the age of 80. We were surprised that physical signs of central nervous system disorder had so adverse, and cardiovascular disease, even heart failure, so benign, an effect on the outcome. Contrary to expectation, a history of previous attacks was not a favourable prognostic indicator in organic mental disorders. Admission from lonely homes did not, in fact, affect prognosis adversely, and social isolation turned out to be of serious significance mainly in people of 70 or over. We had also not been aware of the lethal effects of certain combinations of clinical findings, which will be described below.

DETERMINATION OF FEATURES OF PROGNOSTIC SIGNIFICANCE

From an examination of the state of the patient on admission as recorded on the case card in relation to the actual outcome, we are now attempting to distinguish features which may prove to be of general prognostic value. There are a number of related features which appear to affect both survival and the possibility of social recovery. It is not possible with so small a number of cases to disentangle these completely, and so determine the specific prognostic effect, if any, of the separate factors. The most that can be done is to present broad differences at first, and to separate out later the possible causes in as much detail as the data permit.

The Association of Age With Survival and Social Recovery

As one would expect, age has a marked effect on the fatality ratios; 15 per cent. of persons aged 60–69 years died within 3 months and 72 per cent. survived at least 12 months; for other ages the figures were, 70–79 years, 30 per cent. and 60 per cent., 80 years and over, 44 per cent. and 46 per cent. The proportions surviving 3 months but dying within 1 year do not vary much with age (60–69, 13 per cent., the other two groups each 10 per cent.). Because of the effect of age on the death ratios it is necessary to consider other prognostic indicators for each age group separately. The youngest age group (85 persons) also shows the best recovery rate with 34 per cent. recovering within 3 months and 18 per cent. in the subsequent 9 months. In the group aged 70–79 years the figures were 12 per cent. and 10 per cent. of 93 cases, and in those aged at least 80 years, there were only 10 per cent. and 3 per cent. of recoveries in the first 3 and subsequent 9 months respectively. With rising age, functional psychiatric symptoms, whether alone or as an admixture of organic mental reactions, became increasingly rare. In persons under 70 years of age 26 per cent. had a functional psychosis, 42 per cent. a mixed organic and functional psychosis and 32 per cent. had an organic psychosis showing no functional symptoms; in the age group 70–79 years the proportions were 9 per cent., 39 per cent. and 52 per cent. respectively, and in those aged at least 80 years, 3 per cent., 18 per cent. and 79 per cent. respectively.

Sex Differences With Regard to Survival and Social Recovery

Among male patients (75 in all) 40 per cent. died within 3 months, 15 per

cent. after 3 but within 12 months and 45 per cent. survived at least one year. The corresponding figures for 142 females were 20 per cent., 9 per cent. and 71 per cent. But these differences, which are highly significant ($P < 0.01$)* do not necessarily indicate an intrinsic sex difference.

The fact that there were relatively more women in the younger and relatively more men in the higher (80 plus) age groups does not account for these sex differences, since, age for age, the male fatality ratios were higher than those of females. But only 24 per cent. of the men were in good general health, whereas 59 per cent. of the women were physically fit. While there was no significant difference between the fatality ratios of men and women suffering from cardiovascular disease, among those with a central nervous lesion alone 70 per cent. of the men and 43 per cent. of the women died within 12 months, and this difference is highly significant; it is not due to a preponderance in this group of old men over old women, since the proportions among men and women with such lesions in the three age groups are similar ($P > 0.05$). There is no significant difference between men and women with regard to social recovery, 27 per cent. of the former and 35 per cent. of the latter recovering within one year of admission.

Survival and Recovery Rates for the Three Diagnostic Groups

The functional psychoses have the best prognosis both in respect of survival and recovery, and the psychoses with no functional signs the worst. Of those with a functional disorder, 87 per cent. survived at least one year and 68 per cent. made a social recovery within one year; among those with a mixed organic and functional psychosis, 78 per cent. survived one year and 44 per cent. recovered in that time; among the purely organic psychotics the corresponding figures were 43 per cent. and 12 per cent. These differences are not just due to differences in age distribution in the three diagnostic groups since similar differences are exhibited between the three groups in each of the age groups.

Other Clinical Features Affecting Survival and Recovery

The presence of *positive psycho-organic symptoms* (confusional states) was of bad prognostic import. Of 103 persons with these symptoms 42 died within 3 months and 11 after 3 but within 12 months, whereas of 83 patients not exhibiting these symptoms the figures were 14 and 11 respectively. The difference in prognosis during the first 3 months between patients with and without positive psycho-organic symptoms are highly significant ($P < 0.01$).

Evidence of *focal lesions in the central nervous system*, which included dysphasic symptoms, unless they appeared to be part and parcel of a general dementia, but excluded inconstant tremors, rigidities, resistances and absence of tendon jerks as isolated findings, also had a bad prognostic significance: of the 82 patients with neurological lesions 30 died in the first 3 months, 16 during the next 4–12 months, and only 36 survived the first year. In the group exhibiting both functional and psycho-organic mental symptoms there were significantly more deaths and fewer social recoveries among those with focal lesions of the

* In this paper, where statistical tests of significance have been applied, the results have been indicated in brackets, e.g. ($P < 0.01$) or ($P > 0.10$). The former means that the odds *against* obtaining the observed differences by chance are at least 100 to 1, and the latter that the odds are only 10 to 1 or less *against* chance effects. The borderline between values of P considered to be statistically significant or not is, by custom, arbitrarily defined, and in this paper the maximum value of P considered to indicate statistical significance is $P = 0.02$, that is to say that the odds against chance effects are at least 50 to 1 before the groups are considered to show significant differences.

central nervous system ($P < 0.01$); in the purely organic groups there were also more deaths and fewer recoveries among patients exhibiting such lesions, but not to a significant extent ($P > 0.05$). The co-existence in the same patient of positive psycho-organic symptoms and abnormal findings in the central nervous system did not aggravate the prognosis significantly. In both mixed and pure organic groups, patients classified as exhibiting *definite dementia* had lower recovery rates than those in whom dementia was mild or doubtful.

A history of a *previous psychiatric illness* from which recovery was made was found in 19 (61 per cent.) of the 31 functional psychotics, in 24 (32 per cent.) of 79 persons with a mixed psychosis and in only 9 (8 per cent.) of the 107 persons classified as suffering from a purely organic psychosis. In none of the three diagnostic categories was a significant difference in outcome found between those with and those without a history of previous illness. However, it should be noted that a history of previous mental illness from which a recovery has been made is significantly more common in functional psychotics than in the other diagnostic groups, and as we have seen above a functional illness had a better prognosis than the other types. To the extent that a previous history of mental illness indicates a likely diagnosis of functional psychosis in cases where perhaps little other information is forthcoming, it can be used indirectly as a prognostic indicator. In those cases where a firm diagnosis can be made, a history of previous illness will not give any additional information about prognosis.

Social Factors

There remain to be discussed several social factors that had been considered at the beginning of this investigation to be potentially significant in making a prediction of social recovery.

The *civil state* did not appear to affect the speed of social recovery at all as the proportions of persons recovering in less than 3 months and in 3 to 12 months were similar in the three categories, married, widowed and single. Hospital admission for elderly persons with some mental derangement does not necessarily imply sudden or serious deterioration. It often happens that for social reasons the continuation of home care has become impossible. For similar reasons, discharge is sometimes precluded not by the clinical state but by *domestic arrangements*. However, in a comparison between patients who had been living alone, as inmates of institutions, with their spouse or with friends, we find that the proportions recovering in less than 3 months and in 3 to 12 months are similar ($P > 0.10$): 20 per cent. recovered within 3 months and 12 per cent. in 3–12 months: in 68 per cent. recovery had not taken place by the end of the year.

It is well recognized that living arrangements do not necessarily reflect the *social adjustment* of elderly people, and that it is possible for an old person to be socially isolated even while living in the "bosom of the family". In our material, severe, unquestionable social isolation was found in only 54 of 217 patients, the proportions being similar in males and females. Whereas 23 per cent. of the 163 socially integrated persons recovered in less than three months and 14 per cent. in the next nine months, the corresponding figures for the socially isolated were 13 and 4 per cent. respectively. These differences in outcome are statistically significant ($0.02 > P > 0.01$). The association of social isolation and low recovery rate was however confined to the age groups 70 and over. Examination of our data shows that at this age social isolation was nearly always associated with a severe dementing illness, which itself rendered discharge from hospital

unlikely. In the decade 60-69 it was found more often in conjunction with functional or mixed states, and did not delay recovery.

Summary of Indicators of Survival

Summing up this review of factors affecting survival, it is suggested that the higher death-rate among men is largely due to a heavier incidence among them of serious physical diseases; cardiovascular disorder was less common than were abnormal findings pointing to damage of the central nervous system. This great frequency of neurological abnormalities in old people with psychiatric disorders was not unexpected, but their serious import in shortening the duration of life even more than cardiovascular disease, including many cases with heart failure, reminds one of the indispensability of an intact brain for the mere survival of the organism. The state of physical health was more important as a prognostic indicator in the 60-69 years age group where the differences in survival between those in good and bad health were highly significant. The differences in the group 70-79 years were smaller, and were of no importance in the 80 years and more age group. Among patients who had remained sufficiently well integrated intellectually and emotionally to react with neurotic, affective or paranoid behaviour patterns in the presence of organic mental symptoms, death was much less frequent in the early stages of the illness.

Summary of Indicators of Social Recovery

Discharge from mental care was rare when there were physical conditions causing early death. Severe social isolation was associated with poor chances of recovery in the higher age groups. Within each diagnostic category, the younger patients tended to recover more often than the older. Neither civil state nor domestic arrangements had any effect on outcome. Unexpectedly, a history of previous attacks did not influence prognosis, except in so far as it was rarely found in the purely organic group, which had the most unfavourable outcome.

Finally, we confirm that the psychiatric diagnosis, even if only expressed in very general terms, remains a reliable indicator of the eventual outcome. Social recovery within one year occurred in 21 of 31 patients with uncomplicated functional psychoses; it was encountered in only 13 of 107 patients with simple organic psychoses. In the intermediate group of patients, who exhibited symptoms and signs of both the organic and the functional mental reaction types, social recovery occurred in 35 of 79 cases (Table I). However, this mixed group was also younger than the purely organic one, and contained a much higher proportion of patients in whom organic mental changes were only mild or doubtful. In comparing the mixed and the purely organic groups allowance must, therefore, be made for differences in age and severity of organic changes; after doing this, we still find differences in outcome between patients with simple organic dementias and those with mixtures of functional and organic mental reaction types, but the higher recovery rate of the mixed cases fails to reach statistical significance. Twenty-eight patients were allocated to the mixed group solely on account of mild or doubtful evidence of organic mental impairment, and their recovery rate (61 per cent.) did not differ significantly from that of the clear-cut functional cases (68 per cent.).

Two tentative suggestions emerge from all this: (1) so-called mild and early dementia may be less important prognostically than might be assumed from the amount of attention usually focussed on its discovery; (2), even in the presence of psycho-organic signs, a patient's ability to "produce" a functional psychiatric picture will often indicate preservation of the personality, which may make recovery possible—at least at a social level.

ASSESSMENT OF THE USEFULNESS OF THE PROGNOSTIC INDICATORS SUGGESTED BY THIS ENQUIRY

It is obvious that the clinical features discussed above are not always independent of one another. To take an example: is the good prognosis associated with functional disorders mainly due to the comparative youth of persons suffering from these disorders? Or is the converse true, and age of little importance as compared with absence of organic mental symptoms? Or do both of these, together with other features present in these cases, influence prognosis favourably?

With a very much larger sample it might have been possible to sub-divide the groups and eliminate all possible prognostic factors except the one being tested. This method is not feasible here. From the evidence of our sample we have picked out certain features which appeared to be of prognostic significance. To test their usefulness in prognosis we shall compare the outcome in respect of survival on the one hand, and social recovery on the other, in patients exhibiting none, one, two, etc. of the characteristics which had impressed us as being prognostically important as the result of our follow-up analysis. Before evaluating combinations of these not immediately obvious prognostic indicators, we should point out that some of our initial views on prognosis have been confirmed, especially the bad import of serious physical illness and of acute confusional behaviour disorders ("positive psycho-organic symptoms"), and on the other hand, the relatively favourable outlook in purely functional psychoses.

Indicators Predicting Death Within Three Months

Three factors appeared to be related to an unfavourable prognosis; they were: (i) age of at least 80 years; (ii) focal lesions of the central nervous system; (iii) the presence of psycho-organic symptoms with *no* functional symptoms. The material is insufficient for the effect on the outcome of each of these unfavourable factors, and of all their possible combinations, to be considered separately. But the effect of different combinations is roughly the same, provided there are the same number of factors present. It is found that the chances of survival tend to be inversely proportional to the total number of factors. Table II demonstrates

TABLE II
The Effect of Prognostic Indicators on Survival

Number of Indicators Present*	Men						Women					
	Death Within 3 months		Survival for at least 3 months		Total		Death Within 3 months		Survival for at least 3 months		Total	
	No.	Per cent.	No.	Per cent.			No.	Per cent.	No.	Per cent.		
Three	3	50.0	3	50.0	6		4	50.0	4	50.0	8	
Two	14	53.8	12	46.2	26		12	32.4	25	67.6	37	
One	11	47.8	12	52.2	23		8	20.5	31	79.5	39	
None	2	10.0	18	90.0	20		4	6.9	54	93.1	58	
All patients ..	30	40.0	45	60.0	75		28	19.7	114	80.3	142	

* Indicators of early death are: (i) Age at least 80 years. (ii) Focal lesions of central nervous system. (iii) Psycho-organic but no functional symptoms.

this fact, which is true for each sex. The differences in the death ratios of patients grouped according to the number of these factors which they exhibit have been tested by the χ^2 method and found to be highly significant ($P < 0.01$ for

both men and women). Thus on the basis of this sample we should predict that women under the age of 80 years, with no lesions of the central nervous system and at least one functional symptom, have a good chance (19 in 20) of living for at least 3 months after admission; whereas males showing none of the other indicators of bad prognosis have a 9 in 10 chance of surviving 3 months. The fatality ratios of men are worse than those for women with a corresponding number of unfavourable indicators.

Indicators Suggesting that Social Recovery Will not take Place Within Three Months

The results we have discussed hitherto lead us to suggest the following characteristics to be indicative of a bad prognosis with respect to social recovery: (i) age of at least 70 years; (ii) focal lesions of the central nervous system; (iii) the presence of psycho-organic with *no* functional symptoms; (iv) social isolation; (v) no previous history of mental illness. In the whole sample only 20 per cent. made a social recovery within 3 months of admission and here, too, recovery rates within that period were inversely proportional to the number of characteristics exhibited by each person (Table III). Men who had none or

TABLE III
The Effect of Prognostic Indicators on Social Recovery

Number of Indicators Present*	Men					Women					
	Social Recovery Taking Place				Total	Social Recovery Taking Place				Total	
	Within 3 months		Not Within 3 months			Within 3 months		Not Within 3 months			
	No.	Per cent.	No.	Per cent.		No.	Per cent.	No.	Per cent.		
Four or five	..	0	0.0	23	100.0	23	1	2.9	33	97.1	34
Three	..	5	21.7	18	78.3	23	4	11.1	32	88.9	36
Two	..	4	25.0	12	75.0	16	6	20.0	24	80.0	30
One or none	..	5	38.5	8	61.5	13	19	45.2	23	54.8	42
All patients	..	14	18.7	61	81.3	75	30	21.1	112	78.9	142

* Unfavourable indicators for social recovery: (i) Age at least 70 years. (ii) Focal lesions of central nervous system. (iii) Psycho-organic but no functional symptoms. (iv) Social isolation. (v) No previous mental illness.

only one of these indicators made an early recovery in 38.5 per cent. of the cases, whereas none of those exhibiting 4 or 5 factors recovered in 3 months. Although there is a clearly defined inverse relationship between the recovery rates of men and the number of features they exhibit, the differences between the diverse groups are only on the borderline of statistical significance ($0.02 > P > 0.05$). However, the same effect is also noted among women, 45.2 per cent. of those with no indicator or only one indicator and only 2.9 per cent. of those with 4 or 5 recovering within 3 months, and in this case the differences between groups are highly significant ($P < 0.0001$).

CONCLUSION

It is not proposed that clinical methods of assessing prognosis in the individual patient should be entirely replaced by a primer of prognostic pointers. But our data suggest that when suitable disposal of large numbers of patients

is at issue, fewer errors are likely to be made if adequate account is taken of certain characteristics which affect outcome unfavourably. Those we have defined are relatively easy to assess after only a short period of observation. This is particularly true of the factors which we think are prognosticators of early death. In another study (Norris, in preparation), one of us found that of persons of all ages transferred from observation units to mental and other hospitals, 5 per cent. of male and 3 per cent. of female transfers died within 28 days of transfer. Among transfers over 65 years of age, 16 per cent. of males and 5.5 per cent. of females died within 28 days of transfer. If therefore, by making an informed guess about the likelihood of early death, we save some persons unnecessary transfer shortly before death then a study of prognosticators is of value. Likewise, an early selection of patients who are most likely to recover from the current attack of mental disorder and who would therefore benefit greatly by transfer to hospitals providing modern psychiatric treatment is a goal worthy of attainment.

SUMMARY

This study shows that after an observation period not exceeding 10 days it was possible correctly to predict death, or discharge from mental care, during the subsequent year, in about three-quarters of patients over sixty ($N=217$) admitted to a mental observation unit.

When arriving at a prognosis, account was taken in each case of: age, sex, civil and domestic status, social adjustment, physical health, previous psychiatric breakdown, and the presence of functional and psycho-organic mental symptoms.

Serious physical illness, acute organic-confusional states, and age over 80, were the main conditions associated with death within the year; 40 per cent. of cases with acute confusion died within 3 months. Discharge from mental care was rare in the presence of definite dementia, or of severe social isolation before admission. The outlook for patients with purely functional disorders was good both for survival and for recovery. Those showing mixed syndromes had an intermediate prognosis; mild intellectual impairment did not appear to affect the outcome, but definite dementia rendered recovery unlikely.

The attempt to predict death or recovery within 3 months from admission was unsuccessful. An analysis of our data in retrospect showed that insufficient weight had been placed on the following characteristics as indicating early death, when two or more were present in the same patient: male sex; age of 80 years or more; focal central nervous system lesions; absence of functional symptoms in an organic psychosis. Early recovery was unusual, but occurred in about 50 per cent. of those under 70 years of age, with functional symptoms as part of the clinical picture, history of recovery from previous attacks, absence of focal central nervous system lesions and adequate social contacts before admission.

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AFFECTIVE DISORDER ARISING IN THE SENIUM

II. PHYSICAL DISABILITY AS AN AETIOLOGICAL FACTOR

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In previous papers (Roth and Morrissey, 1952; Roth, 1955) evidence for the importance of affective psychosis in old age was presented. It was shown further that in some half of those admitted after the age of 60 no attacks had occurred before this age, and that no new aetiological factor such as cerebral degeneration was associated with these cases of late onset (Kay, Roth and Hopkins, 1955). The problem is to elucidate why it is that defences against illness effective throughout most of these patients' lives prove inadequate in old age. Now in the study just referred to, a tendency for physical illness to be commoner in patients having their first attack after 60 was noted. A more detailed analysis of the incidence of physical illness in the two groups has therefore been carried out in order to investigate its possible aetiological role in old age affective disorder.

METHOD AND SELECTION OF MATERIAL

During a two-year period the case records of all admissions aged 60 and over were examined, and in addition about one-quarter were seen personally by one of us (D.W.K.K.). Cases with affective disorder were selected on the basis of a *manic or depressive symptom-complex* of at least a few weeks' duration. Those in which affective symptoms merely coloured a clear-cut organic psychosis were excluded. Out of a total number of 474 admissions, 231 satisfied these criteria. In order to determine if patients with onset late in life showed more or less physical illness than the others, the 231 cases were divided as in the previous study into two sub-groups as follows:

1. An early onset group whose first attack occurred before the sixtieth birthday.
2. A late onset group whose first attack or onset of illness occurred later.

Any incidence of physical illness in the group of early onset, in whom a tendency to affective disorder had already become manifest, is likely to be fortuitous or at the most suggest that somatic disease was one of the stress situations liable to bring about a recurrence of symptoms in predisposed individuals. A similar incidence in the group of late onset could likewise be coincidental or be due to the fact that physical illness plays some role in precipitation. A much higher incidence, if not due to age, would on the other hand suggest a closer aetiological relationship in the late onset group, which could be further investigated by a more detailed analysis of the differential incidence of the various kinds of illness and study of the individual cases.

Sex Distribution. There were 28 males and 92 females in the early, and 49 males and 62 females in the late onset group (Table I).

TABLE I

Distribution of 231 Consecutive Cases with Affective Disorder Admitted During a Two-year Period, (i) by Age of Onset, (ii) by Sex; the Mean Ages are Shown

				Males		Females		Total
				Nos.	Mean Ages	Nos.	Mean Ages	
Group with:								
Early onset	..	..		28	68.5	92	65.4	120
Late onset	..	..		49	70.5	62	70.0	111
Totals	..	..		77	69.7	154	67.2	231

Age. The mean age of the early onset group was 66.1, of the late onset group 70.2 years.

Physical Illness. In assessing the frequency and nature of physical illness use was made of: (1) Data in social histories, which were available in about three-quarters of the cases. (2) Clinical examination. (3) Routine laboratory tests carried out on admission (full blood count, sedimentation index, blood bromide, blood urea, fasting blood sugar, Kahn, urine analysis). (4) Special investigations such as X-rays and electrocardiograms, which were carried out where indicated. (5) Consultant opinions: many patients were examined by a general physician to assess their fitness for E.C.T.; E.N.T. examination was carried out as a routine; and patients were referred to the ophthalmologist whenever there were visual symptoms. Follow-up studies carried out on all patients have usually settled the issue in cases of doubt.

Classification of findings. The authors have been responsible for the classification and interpretation of the data available. All cases of physical disorder have been included, except: varicose veins, herniae, osteoarthritis and joint deformities, congenital or long-standing non-progressive neurological defects, and chronic bronchitis and emphysema, unless these disabilities were sufficiently severe for special treatment to have been recommended. Terminal bronchopneumonia and peripheral arteriosclerosis were also excluded.

Where necessary, cases were included under more than one heading; these cases are also referred to separately under Multiple Disabilities.

RESULTS

The overall incidence of physical illness of all kinds was 63 per cent. among males and 51 per cent. among females; in the early onset group the corresponding figures were 50 per cent. and 42 per cent., and in the late onset group 71 per cent. and 65 per cent. Physical illness is thus commoner in the group of late onset ($P < 0.01$); but to evaluate the meaning of this, a more detailed analysis of the incidence of different types of illness in the two groups according to sex is necessary.

1. Acute Physical Illness or Stress

(1) *Acute physical stresses.* These events, which included acute fevers, operations and accidents, could be dated exactly, and occurred in a setting of normal or almost normal mental health. They were recorded whenever psychiatric breakdown took place contemporaneously, or during the immediate convalescent period. When physical recovery was incomplete (e.g. following prostatectomy), the case was also included under the next heading.

TABLE II

Frequency of Acute Physical Stress at Start of Psychiatric Disturbance in Two Groups with Affective Disorder of Early and Late Onset (numbers in brackets). The Differences Between the Groups and Between the Sexes are not Statistically Significant ($P = > 0.05$)

		Males		Females	
		Illness	No illness	Illness	No illness
Early onset group	..	29 (8)	71 (20)	12 (11)	88 (81)
Late onset group	..	18 (9)	82 (40)	23 (14)	77 (48)

Table II shows the frequency of this kind of illness in males and females in the two groups. No significant differences were found between the groups, or between the sexes. Further examination shows, however, that there was, among males, a difference in the severity of the condition present in the two groups. Out of 9 cases in the late onset group, 7 had undergone operations which were, moreover, merely episodes in the course of chronic ill-health. On the other hand, of 8 patients in the other group, only 2 had undergone operations, the rest having suffered from acute febrile illnesses of relatively minor kind. In the case quoted below, a first attack of mania, probably with some initial clouding of consciousness, occurred immediately after operation and considerable blood loss; the subsequent history showed, however, that a chronic underlying disease was present.

Case 1.—A manager, aged 65, who had had a successful and healthy life, was admitted on 24 August, 1951, 8 days after a prostatectomy carried out as treatment for haematuria. Post-operatively, blood transfusion was required. The onset of the psychosis was very acute, with press of talk, bouts of shouting, persecutory delusions of a fleeting kind, and visual and auditory hallucinations.

On admission.—Albumin and pus in urine. Mentally, he was garrulous and expansive. Orientation correct, memory adequate. He recovered gradually from his attack of mania, and was discharged on 16 December, 1951.

Follow-up.—Died 31 July, 1953, after operation for removal of stone in bladder. Cause of death given as: Uraemia, Pyelonephritis, Vesical calculus. There had been no recurrence of mental symptoms.

The greater degree of physical stress necessary to precipitate breakdown in those who have remained well earlier in life is also shown by the greater prevalence among them of chronic illnesses.

2. Chronic Illness

(2) *Chronic ill-health.* Under this were classed such conditions as hypertensive or arteriosclerotic heart disease, urogenital disease, and cancer; their onset was usually gradual or insidious so that although in most cases they clearly preceded the psychiatric disturbance, the time relations between the two conditions could not always be exactly determined. Signs or symptoms of physical illness were always present on admission to hospital, and often persisted after discharge.

Eighty-nine cases (39 per cent. of the total) showed signs of physical ill-health on admission to hospital; the incidence being 32 per cent. in the early and 46 per cent. in the late onset group, a difference significant at the 5 per cent.

TABLE III

Frequency of Chronic Illness in Two Groups with Affective Disorder of Early and Late Onset (numbers in brackets). The Difference Between the Groups is Statistically Significant ($P = < 0.05$)

		Males		Females	
		Illness	No illness	Illness	No illness
Early onset group	..	28 (8)	72 (20)	33 (30)	67 (62)
Late onset group	..	57 (28)	43 (21)	37 (23)	63 (39)

level. No significant differences were found among the females when all types of illness were included; among the males the late onset group showed a significantly greater incidence ($P = < .002$) (Table III).

The disabilities under discussion varied greatly in their nature and severity; by no means equal importance can be attached to them as aetiological factors. They may be considered under the headings: cardiac disorder; respiratory disease; urogenital disease; and other illnesses (Table IV).

TABLE IV

Varieties of Chronic Illness (excluding Sensory Defects) in Two Groups with Affective Disorder. Figures are Percentages, Showing Proportions of Affected Individuals in Each Group

	Cardio-vascular disease		Urogenital disease		Other conditions, e.g. lung, C.N.S. and Neoplastic diseases		Multiple disabilities		Total incidence	
	M	F	M	F	M	F	M	F	M	F
Early onset group	11	10	4	10	22	14	7	5	28	33
Late onset group	22	15	18	10	40	21	24	10	57	37

(1) *Cardiac disease or disorder* occurred in 32 cases, the main conditions being: hypertensive heart disease or cor pulmonale (19 cases), angina of effort (8 cases), auricular fibrillation (5 cases). The criteria for inclusion were, congestive failure, marked dyspnoea, angina, or auricular fibrillation with rapid pulse. Cases with hypertension alone or with clinical or radiological evidence of cardiac enlargement without other signs, were not included. Congestive failure was present in 18 and marked dyspnoea of exertion in 15. Electrocardiographic abnormalities indicating conduction defects were present in 11. Twelve patients were digitalized and several others treated for angina pectoris. E.C.T. was employed in 7 only; 14 others at least would probably have received E.C.T. but were regarded, after consultation with a physician, as physically unfit despite the availability of muscle relaxants. Cardiac disease was relatively predominant in the late onset group and, particularly among males, appeared to be a factor in the development of the affective disturbance as in the following case:

Case 2.—A professional man, aged 69, had always been moody and hypochondriacal but had never before broken down. He was admitted voluntarily on 28 September, 1951, with a four years' history of increasing depression, fits of weeping, and fears of dying. He had attended many doctors with a multitude of physical complaints. Haemorrhoidectomy aged 60; cholecystectomy and appendicectomy aged 68.

On admission.—B.P. 210/90. Marked peripheral arteriosclerosis. Chest emphysematous. Depressed and grossly hypochondriacal; florid bowel complaints; some breathlessness, and ill-defined chest symptoms. He improved after 5 E.C.T. and was discharged.

Follow-up.—In April, 1952, he had a coronary thrombosis. Recurrence of mental symptoms soon afterwards necessitated readmission on 3 September, 1952. E.C.G. showed evidence of cardiac infarction. He was still grossly hypochondriacal, but on this occasion cardiac symptomatology predominated. He developed congestive failure after another coronary thrombosis, and died on 12 December, 1952. Post-mortem refused.

In retrospect, it seems almost certain that some of his earlier symptoms had had their basis in coronary artery disease, and that they could have been alleviated by treatment.

(2) *Respiratory disease* was uncommon, other than as part of the syndrome of cardiorespiratory disorder; mild cases of chronic bronchitis and emphysema are not included. There were 12 cases in all. Chronic bronchitis and asthma with severe dyspnoea was found in four; one of these was a publican's wife, aged 72, who suffered from alcoholism and made a suicidal attempt after

the death of her husband. There were two patients with advanced emphysema, and four others with chronic respiratory disease; silicosis was present in an ex-miner who had previously, when 34, become depressed on being discharged from the pits with miners' nystagmus; many years later he suffered from shortness of breath, but did not again fall ill mentally until after prostatectomy. There were two cases with bronchiectasis, both having acute exacerbations; one case with a chronic discharging sinus from an empyema; and one with a symptomless diaphragmatic hernia which was, however, thought to contraindicate E.C.T. There were no significant differences between the two groups.

(3) *Urogenital disease.* This condition has an obviously different implication in the sexes. Among females, in whom the incidence was 10 per cent., it was as a rule a symptomless urinary infection, discovered only on routine examination, and apparently related to emaciation and neglect. In no case was evidence of more serious disease forthcoming on further investigation or follow-up. The groups were equally affected.

Among males, the incidence was 12 per cent. Prostatic disease was invariably present, and 6 of the 9 cases had undergone prostatectomy; another patient had a prostatic carcinoma from which he later died, although recovering from his depression. All except one fell into the late onset group; this was a man aged 73, whose previous attack at the age of 55 had followed cataract extraction; during his present illness, in addition to prostatic disease, he suffered from failing vision and hearing. Our results appear to show that surgery in prostatic disease may involve a considerably greater risk of initiating affective disorder late in life among males than is generally recognized.

(4) *Other illnesses.* These consisted of: 8 cases of bone or joint disease; 7 with Parkinsonian or other neurological abnormality; 3 with thyroid adenomata; 2 each with exfoliative dermatitis, diabetes mellitus, gastro-intestinal disease, chronic purulent antral infection, post-herpetic facial neuralgia, and painful haemorrhoids requiring operation; and one each of intermittent claudication, painful urethral caruncle, cystic mastitis, leukaemia, gingivitis, severe varicose ulcerations of legs, rectal prolapse requiring operation, and enormous bilateral inguinal herniae impeding movement. There were 8 cases of carcinoma (including rodent ulcers and skin epitheliomata) in addition to the case of prostatic cancer. Twenty-three females and 20 males, of whom 17 belonged to the early and 26 to the late onset group, are included under this heading.

The possibility that there is an association between organic cerebral degeneration and affective disorder arising late in life has been fully considered elsewhere, and rejected (Kay, Roth, Hopkins, 1955). Only 7 cases with signs of neurological disease were found in this material, and these were nearly evenly distributed between the two groups.

3. *Auditory and Visual Defects*

There were 22 cases of moderate or severe deafness and 15 with visual defects; in 7 both defects were present so that 40 individuals were affected. Cataracts accounted for the visual defects in 10 cases, and macular degeneration, diabetic retinitis, post-herpetic scarring and glaucoma in the remainder. Fourteen patients belonged to the early and 27 to the late onset group, the difference being significant ($P = < 0.05$) (Table V).

MULTIPLE DISABILITIES

Thirty-eight patients fell into two or more categories of illness; of these, 25 (23 per cent.) belonged to the late onset group and only 13 (11 per cent.) to the

TABLE V

Frequency of Sensory Defects Among Two Groups with Affective Disorder of Early and Late Onset. Figures are Percentages of the Total Numbers of Each Sex in Each Group (numbers given in brackets). Taking the Sexes Together the Incidence of Defects is Significantly Greater in the Late Onset Group ($P = < 0.05$)

		Males		Females	
		Visual	Hearing	Visual	Hearing
Early onset		7 (2)	14 (4)	6 (5)	6 (5)
Late onset		14 (7)	10 (5)	16 (10)	15 (9)

other group. This fact again illustrates the greater amount of physical illness in the former. One member of this group, was a widow of 73 whose first attack of depression was associated with post-herpetic neuralgia, loss of vision in one eye, and hypertensive heart disease. A first attack occurred in a man of 86; there was a chronic irritating dermatitis, and failing vision, due to senile macular degeneration. In a male of 65 physical activity had been severely restricted for a few years, first by rheumatoid arthritis, and later owing to congestive heart failure.

RELATIONSHIP BETWEEN SEX AND PHYSICAL ILLNESS

Although the frequency of acute stress at the beginning of psychiatric disturbance is not significantly different in the two groups in either sex, yet it is clear that among males, those in the late onset group suffer from more serious conditions, which either lead to, or are episodes in the course of, chronic ill-health. Chronic illness of each kind shows a higher incidence among males of late than of early onset and when all types are combined the difference is statistically significant ($P = < 0.01$). Among females similar differences exist without reaching the level of statistical significance. The association between physical illness and affective disorder commencing in late life is evidently more clearcut in the male sex.

Physical Illness and Age. Since the incidence of physical disability tends to increase with age, the possibility that the difference found might be due merely to the different mean ages of the two groups and not related to the psychiatric disorder has to be considered. However, when the material is divided into five-year age groups the differences in incidence of physical illness between the groups of late and early onset remain striking and consistent, in each of the groups under 70 and over 75 years; in the group 70–75 years the incidence in the early and late onset cases was identical. Moreover, when a correction for differences in age between the two groups is applied the expected total incidence of physical illness does not differ significantly from that actually observed in males or females and whether or not sensory defects are included ($P = 0.05$ in each case). Further examination of the data shows that only in the case of visual impairment is there a distribution with age which differs significantly from the random ($P = < 0.05$).

Mortality Rates and Physical Illness. A comparison of the mortality in the two groups revealed that after a mean follow-up period of 82 weeks, 14 patients in the late onset group had died, whereas there were only eight deaths in the other group. Although the difference is not statistically significant, a detailed analysis of the relevant records suggests that it reflects the difference in the incidence of physical illness in the two groups. Thus 16 of the 22 patients who died were suffering from physical illness on admission which was, in fact, the cause of death in nearly every case. In about one-third of these cases the psychiatric illness may itself have made a considerable contribution to death as a result of

exhaustion and inanition; such cases were evenly distributed between the groups. In the remainder the specific physical illness seemed clearly to have been a major factor in the determination of the outcome. It was of some interest in this connection that if the expected mortality rates were estimated on the basis of those of the general population of West Sussex (Registrar-General's Annual Report, 1951) the rates actually observed are found to be significantly higher in the late onset group when the two sexes are combined ($P = < 0.05$), but the difference fails to reach significance for the early onset group. These data offer a further hint that there may be some factor other than age contributing towards mortality which exerts a stronger influence in the group of late onset.

DISCUSSION

The data make it clear that both acute and chronic physical illness are common in affective disorder in old age. Whether or not such illness has a direct aetiological relationship to the affective disorder, its practical importance must be considered, for it is bound to influence the course and outcome of the psychiatric condition. It is particularly important to bear in mind the possibility of complicating physical disorder when evaluating affective illness in old age because the severity or florid nature of the psychiatric symptoms may obscure the presence of associated somatic disease. Even if the patient should complain of somatic symptoms there is some risk of these being attributed to a hypochondriacal self-scrutiny or delusions of a nihilistic kind. It was in fact not uncommon in this material for the physical illness to be overlooked, and in three cases the existence of serious physical disease was confirmed only at autopsy. In a number of other cases pre-occupation with vague chest pains attributed to hypochondriasis proved on follow-up to be associated with coronary artery occlusion and diffuse hypochondriasis with malignant or other chronic illness.

The figures for the incidence of all physical illness in the total material lend considerable force to such facts. Among males with affective disorder it was 57 per cent. and if sensory defects are reckoned, 62 per cent., while in females the corresponding figures were 43.5 per cent. and 51 per cent. No precise comparison with incidence in the general population is possible since there are no published figures based on detailed physical investigation. A survey of average monthly sickness assessed by interview in a sample of the adult population reported by the Registrar-General (Statistical Review of England and Wales for 1949) revealed a very high incidence of physical illness in individuals aged 65 and over, but over four-fifths of this was classified as minor or ill-defined disability which would have been either unrecorded in our notes or excluded by our criteria. Control studies of the incidence of physical illness in the general population from which our cases were drawn are evidently indicated.

But our method permits comparisons between the two direct groups and this suggests that in cases of late onset physical illness played a part in overpowering defences against breakdown that had proved effective during the greater part of life. To consider in more detail the different types of physical disability that have been defined, acute illness was equally common at the onset of the psychiatric disorder in each group. But among males of the late onset group acute illness was far more often of a grave character and prone to be followed by chronic disability than among the group of early onset. Among the females this was not so; yet examination of the case records suggests that here, too, there may have been more stress in the late onset group. Thus 3 patients out of 9 had recently lost their husbands, whereas no such bereavements

had occurred in the other group. We may tentatively conclude that in both sexes, but especially in males, a first attack in old age is associated with a greater amount of stress than is usually found among those who have fallen ill earlier in life.

Turning now to chronic physical illness and sensory defect we find that the group of late onset is much more often afflicted by all the categories defined. The frequency of this kind of illness is in fact extraordinarily high, well over half the male cases being affected. The men show a higher incidence of all categories of illness. Among women there is at first sight little difference between the early and late onset group, but in fact among females with affective disorder of late onset there are more with serious or multiple physical illnesses.

Not all the late onset group were first admissions, a proportion having had previous attacks (though after the age of 60). A detailed analysis of the case records was therefore carried out and this showed that in the great majority of cases of the late onset group the chronic illness identified on the present admission had been present before the very first breakdown. In the remaining cases some other physical illness had been clearly associated with the first attack.

We must now ask if it would be correct to conclude from these facts that the psychiatric disorder is merely symptomatic of the physical disease. But the term "symptomatic psychosis" usually signifies an intimate and specific association between the physical and psychiatric phenomena. It is unlikely that the association here observed is of this kind. Thus 29 per cent. of men and 35 per cent. of women fall ill in old age for the first time without physical illness, and if sensory defects are not reckoned the figures are 35 per cent. and 47 per cent. The psychiatric picture in the great majority of cases was that of a functional affective psychosis independent of any contribution by cerebral disease; nor was there any difference between the two groups in this respect (Kay, Roth and Hopkins, *loc cit.*). Moreover, the physical and psychiatric disorders by no means pursued a parallel course. Thus, in a number of cases the physical illness associated with breakdown continued, but the patient recovered from the psychiatric disorder or improved sufficiently to be discharged; the pattern of outcome of both late and early onset groups, with their high discharge and low mortality rates despite the frequency of physical illness, is in fact that of a benign psychiatric disorder. In other cases the illness improved, as for example, after prostatectomy with subsequent chronic urinary infection, but the patients did not exhibit a corresponding psychiatric recovery.

Hence, we cannot attribute to physical illness any specific aetiological role in relation to affective disorder, whether appearing in old age for the first time, or occurring afresh in senescence. But the relatively high incidence of physical illness in those who have avoided affective illness until old age suggests that in it we have identified *one* aetiological factor of importance. Independent evidence in relation to the possible role of physical illness must obviously be sought. The incidence of affective breakdown among old people admitted to general hospitals must be investigated to ascertain whether this is greater than the normal expectation. And the incidence of physical illness in a sample of old people living outside hospital needs to be compared with that in our affective cases.

Some independent evidence already exists to support the aetiological role of physical illness as suggested by our findings. Dayton (1940) as a result of his large scale statistical studies of admissions to mental hospitals in the U.S.A., has suggested that the incidence of psychoses at all ages is related to that of physical illness and disability in the general population, and that it increases with age in

association with the degenerative changes of later life. He was referring mainly to the senile and arteriosclerotic psychoses. Our findings suggest that there may also be some relationship between physical disability and affective disorder of late onset.

Dayton further suggested that the higher incidence of psychiatric disorder which he found among males of all ages (when account was taken of the sex ratios in the population at risk) was related to their greater physical morbidity and mortality risks, particularly late in life. However, Sheldon (1948), in his survey of a random sample of elderly people living in Wolverhampton, found that among men physical disability was not in fact commoner than among women, and that more robust health was the rule. This interesting observation receives some confirmation in the report on general morbidity in England and Wales (Registrar-General's Statistical Review, 1953), which shows that sickness rates as estimated in a random sample of the general population, are in fact lower for males than for females in all age groups, including the groups 75 and over. Now physical illness is significantly more frequent among males than the females in our material. If, therefore, the sex difference described in the Registrar-General's Statistical Review is a real one the relative incidence in the sexes observed in our affective cases represents a reversal of the trend in the normal population. And this could be interpreted as providing some independent confirmation that the association between physical and psychiatric disorder we have found is unlikely to be fortuitous, but may have aetiological significance, particularly in males. The implication would be that there are differences in the response to physical illness in old age between males and females, there being in the former a greater hazard of complication with affective disorder. Such an interpretation would offer one possible explanation for the significantly larger proportion of males in the group of late onset ($P = < 0.02$). It would seem that physical illness in males, though less common, is more dangerous; they are more likely to die, and also appear to be more likely to suffer from affective illness.

Why this should be so is not clear. A common factor in most of the chronic and miscellaneous conditions described appears to be a tendency to restrict free motor activity; others are irritating and painful; and a few, by their toxic effects, probably lower resistance and general health. It may be that restriction of normal activity is less well tolerated by males whether from innate biological, or cultural reasons, and is more likely to lead to an affective psychosis, which might itself be a contributory cause of their greater mortality. Such a formulation is not necessarily inconsistent with the theory of specific predisposition to affective disorder. The manifestation rate of one in three or four of the gene responsible for this type of illness leaves considerable room for a causal contribution by exogenous factors such as physical illness. But in fact the issue as to whether specific or multifactorial inheritance contributes to the causation of affective disorder is at present undecided (Slater, 1953). These questions are evidently matters for further study.

It might be advisable meanwhile to pay more attention to the risk of affective breakdown in old age as a complication of operations and physical illnesses. Prompt treatment or amelioration of physical disorders in old age might conceivably prove to be of some prophylactic value against psychiatric breakdown. And in all cases of depressive or manic illness in the old a most detailed and rigorous physical investigation must be carried out in an attempt to identify physical illness that may be contributing to causation, particularly in males who before senescence had been immune to mental disorder.

SUMMARY

(1) The aetiological role of physical disability in affective disorder of old age has been studied in 231 consecutive admissions aged 60 and over. The incidence of acute and chronic illness and serious sensory defect was compared in those whose first attack had occurred before 60 (120 cases) and those with a first breakdown after 60 (111 cases).

(2) Physical illness and/or sensory disability was present in 62 per cent. of the men and 51 per cent. of the women in the whole material.

(3) In about one-sixth of all cases acute physical stress (illness, operation, or trauma) immediately preceded the onset of affective breakdown. But in the group with onset after 60, the physical condition was more often an exacerbation of, or consisted in operative treatment for, underlying chronic disease, from which recovery was incomplete.

(4) Chronic physical illness was found in 40 per cent. Nearly every kind of illness, including sensory defect, was commoner in the group with late onset.

(5) These results suggest that more severe stress is necessary to cause affective breakdown in those individuals who have been resistant during most of life. In general, exogenous may be more important than constitutional factors in this group, whereas broadly speaking the reverse may be true of those with earlier breakdown.

(6) The difference between groups of late and early onset is more marked and consistent for males. Physical illness is probably more important in the causation of affective psychosis commencing in old age in men; this may contribute to the higher proportion of males in the group of late onset.

(7) Thorough physical investigation is indicated in all cases of affective disorder commencing in old age particularly in men. Serious organic disease is often present and underlies hypochondriacal complaints.

ACKNOWLEDGMENTS

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CHLORPROMAZINE IN THE TREATMENT OF THE CHRONIC DISTURBED SCHIZOPHRENIC PATIENT

By

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INTRODUCTION

THE pharmacology of chlorpromazine (Anton-Stephens, 1954; Hopkin, 1955) and its use in psychiatric practice (Garmany *et al.*, 1954; Elkes *et al.*, 1954; Charatan, 1954; Labhardt, 1954) have been described in several recent papers. The present paper briefly describes a controlled experiment on the use of the drug in a group of chronic disturbed schizophrenic patients, the object being to introduce as few variables as possible into the experimental situation, with a view to making the results as objective as is ever possible in a psychiatric investigation.

THE EXPERIMENT

In a disturbed male ward of 60 patients, about 40 patients were in the age group 29–50 (average age 35) suffering from schizophrenia, mostly classified as paranoid, of at least ten years' duration. For the purposes of the experiment, these patients were divided into two numerically equal groups, surnames beginning A to L in one group and the remainder in the other, the division, therefore, being clinically random.

The names of the patients were recorded on a large wall-chart in the ward office, and daily against each name was recorded the number of "aggressive" outbursts that the patient had shown and which the nursing staff noted in the course of their normal duties. In order to simplify matters as far as possible for the observers, "aggressiveness" was divided into four categories, A, B, C and D. "A" was defined as being a short verbal outburst, not sufficiently prolonged to merit interference by a nurse; "B" was a more prolonged verbal outburst, which required interference; "C" was a short physical outburst, such as a sudden blow, the physical equivalent of "A", and "D" was a prolonged physical outburst requiring interference by the nursing staff. It was not expected that every "aggressive" outburst could be recorded, but deficiencies in this respect would be of no practical significance in the comparisons between the two groups.

After a preliminary control period of recording of six weeks' duration, each individual of one group was given 50 mg. three times daily of chlorpromazine and of the other group the same number of identical-appearing but inactive tablets. The tablets were administered for six weeks and the recording continued as before.

There was then a rest period of twelve weeks, after which a precisely similar experiment was carried out, with the exception that the dosage used was 100 mg. three times daily and the tablets were administered for ten weeks. The personnel of the groups in the second experiment did not exactly correspond to that of the first, due to unavoidable transfers.

In both experiments the identity of the active and inactive tablets was known only to the hospital pharmacist.

Apart from the giving of the tablets, the normal ward routine remained completely unchanged throughout. The patients were not interviewed any more often than usual by the medical or nursing staff, nor was any alteration made in any regular medication that the patients might have been having previously. The weights of the patients were those recorded normally.

RESULTS

The results are summarized in Tables I and II. Groups X_1 and X_2 received the active tablets, whilst groups W_1 and W_2 were the controls. It will be seen that there is no significant change in the recorded aggressive incidents of any type in groups X_1 and X_2 following a dosage of 150 mg. or 300 mg. daily of chlorpromazine orally, respectively. There is, however, in each group a significant increase in body weight, not shown in the control groups.

TABLE I

Patients Given 150 mg. Daily of Chlorpromazine or Equivalent Control Tablets

Group	Period	Number of "Aggressive" Incidents						Average Weight Change at End of Experiment
		Type A	Type B	Type C	Type D	Total	Daily Average	
W 18 individuals (control)	40 days prior to tabs.	160	43	19	2	224	5.5	—
	40 days on tabs.	.. 200	24	13	3	240	6.0	-0.6 lbs.
X 18 individuals (chlorpromazine)	40 days prior to tabs.	83	37	15	1	136	3.4	—
	40 days on tabs.	.. 151	19	10	0	180	4.5	+3.6 lbs.

TABLE II

Patients Given 300 mg. Daily of Chlorpromazine or Equivalent Control Tablets

Group	Period	Number of "Aggressive" Incidents						Average Weight Change at End of Experiment
		Type A	Type B	Type C	Type D	Total	Daily Average	
W_2 18 individuals (control)	14 days prior to tabs.	74	17	2	2	95	6.8	—
	70 days on tabs.	.. 346	31	15	2	394	5.6	+1.0 lbs.
X_2 18 individuals (chlorpromazine)	14 days prior to tabs.	46	8	2	0	56	4.0	—
	70 days on tabs.	.. 243	16	6	1	266	3.8	+4.0 lbs.

DISCUSSION

The difficulty of finding adequate controls, the lack of objectivity and the inability to make quantitative measurements, are only a few of the problems inherent in the investigation of the effectiveness of a drug in psychiatric conditions.

Without control groups, it is impossible to be certain that any change found in the patient is not due partly or totally to the altered environmental factors inherent in an experimental set-up. For example, a series of detailed psychiatric interviews in patients previously neglected, or an awareness amongst the nursing staff and patients that some new drug is being tried, are important changes that cannot be disregarded (Bickford, 1955). Unfortunately, many of the reported experiments on the effect of chlorpromazine seem to have lacked control groups (Charatan, 1954; Garmany *et al.*, 1954; Labhardt, 1954 and many others).

The assessment of improvement by individual interview is also apt to lack objectivity; though with a well controlled experiment (e.g. Elkes *et al.*, 1954), this criticism cannot be sustained.

The present experiment, recording numerically as it does, the occurrences of one particular easily detected symptom, can claim to be objective. It is also controlled in that one group had inert identical-appearing tablets and that the selection of groups was clinically random. Also, the identity of the control group was unknown, but unfortunately side-effects such as dryness of the mouth, gave the nurse-observers a clue as to which were the active tablets.

The most serious source of error in this experiment seems to be in the definition of "aggressive" behaviour. The degree of affective involvement in the noisy or motor outbursts of schizophrenic patients may vary a great deal, so an apparently simple symptom such as a shout, may be an expression of differing psychopathological states. Objection, too, might be taken to the different "degrees" of aggressiveness, as defined above, but these were of no importance in the final result.

The finding that, in this controlled experiment, chlorpromazine, even in a dosage of 300 mgm. daily, made no significant difference in the aggressive psychomotor behaviour of chronic schizophrenic patients, is interesting in that it is not supported by the findings of other observers who, however, often found that the schizophrenic group was the least responsive to the drug (Lehmann, 1954; Elkes *et al.*, 1954) and that the more chronic schizophrenics showed a worse response than the more recent ones (Labhardt, 1954). On the other hand Labhardt (1954) also showed that the paranoid schizophrenic group gave a far better response than any other schizophrenic group, the improvement rate being as high as 60 per cent. in an uncontrolled experiment.

Finally, the writer makes no apology for the apparent crudity of this experiment. The patients are grouped together as disturbed schizophrenics, a crude symptom is recorded and untrained observers are used to record it. But to have attempted to separate the patients into different categories or record groups of elaborate symptoms, would have been to have destroyed the whole object of the experiment, which was to record the effects of the drug in a group of patients in which all other factors remained unchanged.

CONCLUSION

The findings in the present experiment suggest that environmental factors may play a bigger part in the apparent effectiveness of chlorpromazine than is realized and stress that care should be taken in prescribing a drug that is by no means a panacea, lest its reputation should suffer unnecessarily.

There would also appear to be need for more experiments similar to this to be carried out on a larger scale and more carefully controlled than has been possible here.

SUMMARY

An experimental method of assessing the effect of chlorpromazine on symptoms of aggression in male chronic schizophrenic patients is described and it is concluded that statistically there is no change in the symptoms following a dosage of chlorpromazine of up to 300 mg. daily by mouth.

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INTENSIVE CORTISONE THERAPY IN SCHIZOPHRENIA

By

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CORTISONE therapy has been claimed to produce favourable results in clinical schizophrenics (Cohn and Karnosh, 1951; Cohn *et al.*, 1953). Rees and King (1952) carried out a controlled investigation on the effects of Cortisone given in moderate doses over a four-day period to a group of schizophrenic patients and found no significant changes in symptomatology, behaviour or in a series of psychological and physiological tests.

In a personal communication Dr. Cohn suggested that Cortisone given in higher doses over a longer period would probably be therapeutically more effective in chronic schizophrenia.

The present paper describes a controlled investigation into the therapeutic effects of Cortisone given in high dosage over a relatively prolonged period.

EXPERIMENTAL GROUP

The investigation was carried out in a group of 18 schizophrenic patients consisting of nine pairs matched for age, sex, clinical status, duration of illness and previous treatment.

METHODS

1. *Clinical Assessment*

A detailed assessment of clinical status was carried out on all members of the group. An item sheet of some 200 items relating to social, family and personal history, personality, aetiology and symptomatology, was completed for all patients. The various aspects of schizophrenic symptomatology were rated in a 7 point scale by the method of Rees (1949). This detailed analysis of clinical status enabled accurate matching of patients into pairs. One member of the pair received Cortisone therapy and the other was utilized for control purposes.

Clinical data relating to each group on the Item analysis shown in Table I.

2. *Assessment of Recovery or Improvement*

In addition to the above detailed clinical assessment, a modification of the Worcester State Hospital Psychiatric Rating Scale was used. The rating rate consists of 14 traits relating to behaviour and symptomatology which can be rated and scored in terms of deviation from the patients pre-psychotic state.

This method provides a quantitative method of expressing and recording a patient's behaviour and clinical state. The sum total of the scores gives a convenient index of abnormality. The rating scale completed before, during and after treatment, provides a graphic standardized method of recording any

TABLE I

	Per cent.	Symptomatology	Per cent.
Sex:		Introversion rating:	
Male	77	High	88
Female	23	Low	11
Age:		Intellectual disconnection rating:	
20-29 years	77	High	66
30-39 years	11	Moderate	22
39-40 years	11	Low	11
Family history		Emotional disconnection rating:	
(Parents and siblings):			
Negative	67	High	22
Psychosis	22	Moderate	11
Neurosis	11	Low	77
Personality:		Conduction disconnection rating:	
Stable	33	High	66
Somewhat unstable	33	Moderate	11
Very unstable and ill-adjusted	33	Low	22
Onset:		Paranoid disposition rating:	
Sudden	22	High	55
Prodromata then acute	11	Moderate	22
Gradual	77	Low	33
Aetiology:		Type:	
Psychological causes im-		Simple	11
portant	22	Catatonic	33
Exogenous factors contributing	11	Paranoid	55
Mainly endogenous	77		

changes in clinical status or symptomatology during the period of observation.

In view of the importance of multiple recording in investigations of this kind, doctors' and nurses' reports made independently of the above were available for the final assessment of results.

3. Psychological Tests

The tests used in our previous investigations (Rees and King, 1952) were included in the present investigation.

(a) Personal tempo:

- I. The number of triangles that could be drawn in 30 seconds.
- II. Enumeration of objects in 30 seconds, e.g. things to eat, birds, flowers.
- III. Number of responses to coloured Rorschach card in 30 seconds.
- IV. Number of responses to uncoloured Rorschach card in 30 seconds.

(b) Persistence: this was measured by the time the patient could hold out-stretched leg with knee 3 inches above a chair, according to method of Eysenck (1947).

4. Physiological Tests

These included eosinophile counts, blood-pressure readings, water intake and output records, electroencephalography and electrocardiography.

The above tests were carried out before, during and after Cortisone therapy.

CONTROL PROCEDURE

In this investigation we employed both the method of paired controls and the method of using the patient as a self control.

The method of paired controls in psychiatry presents inherent difficulties as it may be quite impossible to make certain that the two members of the pair correspond in clinical status and prognosis.

It is of paramount importance to ascertain that the members do not differ in important prognostic indicators. In this investigation the patients were matched by age and sex, symptomatology, duration of illness and previous treatment received. This ensured that the groups did not differ significantly in these important prognostic indicators. In spite of all attempts at detailed accurate matching of patients in the paired series, it remains a possibility that the capacity for spontaneous improvement may still differ in the two groups. It is therefore clearly desirable to institute other controlled procedures as well.

In the present type of investigation, the method of self control is valuable.

This method has recently been described in detail by Hogben (1954).

The following procedures were applied:

Double Blind Trial

In order to avoid the possibility of bias in recording and assessment of the clinical changes on the part of nurses or doctors, the investigation was carried out blind, neither the nurse nor the doctor making the assessment knew when inert or active injections were being given.

The trial can be divided into three phases:

1. Period of inert injections given to all members of the series during which the tests and assessments were carried out.

2. Inert injections continued with the control series and Cortisone therapy given on the other series.

3. Inert injections given to total group.

This method enables the effect of suggestion or therapeutic influence of the general procedure and regime to be assessed and also enables the possibility of spontaneous improvement during the period of the trial to be controlled.

Dosage

The following dosage was used: 8 c.c. (200 mg.) of Cortisone acetate intramuscularly twice daily (400 mg. daily) for 21 days.

8 c.c. saline was given intramuscularly twice daily for seven days before onset of Cortisone administration and for seven days afterwards and in the control series was given throughout the five-weeks trial period.

RESULTS

Six out of nine patients receiving Cortisone therapy showed no significant change in clinical state or behaviour assessed from observation in wards by medical and nursing staff in the more objective method of the Psychiatric Rating Scale. One female patient showed a temporary exacerbation of symptoms returning to previous state after termination of Cortisone therapy.

Two male patients showed a very slight improvement in behaviour and attitude, became more alert and co-operative but without significant change in schizophrenic symptomatology.

One patient in the control series showed a similar slight degree of improvement.

The results are unequivocal and provide no evidence that Cortisone therapy had a significant therapeutic effect on our group of schizophrenics.

No significant changes occurred in psychological tests or electroencephalography.

COMPLICATIONS AND SIDE EFFECTS

In eight out of the nine patients receiving Cortisone, marked side effects occurred usually from 8th–14th day of dosage at 400 mg. The most constant effect was water retention, sudden increase in weight, oedema of dependent parts and, in some, puffiness and oedema of facial subcutaneous tissues.

A tendency to bradycardia was found in four patients, the pulse rate falling to 45–50 per minute after a previous level of 70–75.

When these side effects appeared the dosage had to be reduced and potassium chloride medication by mouth instituted. The dose of Cortisone was later gradually increased again but usually with return of symptoms.

This high dosage therefore imposes a severe strain on the homeostatic mechanisms in the body and these side effects constitute a serious disadvantage.

DISCUSSION

The results of our controlled investigation are unequivocal and provide no evidence to support claims that Cortisone given in high doses over a relatively prolonged period is therapeutically valuable in chronic schizophrenia.

The results are in striking contrast to those of Cohn (1953) who reported that six out of twenty-one chronic patients who had been ill for over six years were discharged from hospital after intensive Cortisone therapy.

He found that paranoid patients showed the best therapeutic response. We were unable to confirm this in our series in which five out of nine patients were paranoid schizophrenics.

Furthermore the marked side effects accompanying continued high Cortisone dosage constitute a severe strain on the organism's homeostatic methods and are a serious disadvantage of this method of treatment.

It is noteworthy that none of our patients developed euphoria which many observers have reported in patients with physical disease during Cortisone therapy and also that only one patient showed exacerbation of symptoms, the majority showing no significant change in symptomatology or behaviour.

It is a possibility that future research may provide an indication for the use of Cortisone in certain selected schizophrenics. Thus if it could be demonstrated that endocrine disequilibrium was causally important in some schizophrenics and that if Cortisone, either by substitution or indirectly by influencing the functions of other endocrines, helped to restore homeostasis in endocrine functions and if this in turn resulted in clinical improvement, a scientific basis for its use in such patients would be established.

It is clear from our results that whatever biochemical, physiological or endocrinological changes are produced by massive Cortisone therapy these did not result in any clinical improvement in our series of chronic schizophrenics.

In conclusion we may say that our findings provide no evidence in support for the general use of this method of treatment in chronic schizophrenia.

SUMMARY

(1) The paper describes a controlled investigation of the therapeutic effects of Cortisone given in high dosage over a period of three weeks.

(2) The experimental group consisted of 18 schizophrenic patients comprising nine pairs matched after detailed clinical analysis for age, sex, clinical status, duration of illness and previous treatment.

(3) The experiment was carried out as a double blind trial, neither doctors making clinical assessments nor nurses knew when active or inert injections were being given. All patients were given inert injections for the first week during which all tests were carried out. Inert injections were continued in the control series for three weeks and Cortisone given to the other series. Finally inert injections were given to both groups.

(4) Psychiatric rating scales, psychological tests of personal tempo and persistence and physiological tests such as blood-pressure and water balance records, electro-encephalography and electrocardiography were carried out before, during and after the period of clinical trial.

(5) No significant clinical improvement was noted in patients receiving Cortisone therapy or in the control series. One female patient showed a temporary exacerbation of symptoms, returning to her previous state after termination of Cortisone.

(6) No significant changes occurred in psychological tests for personal tempo and persistence. In eight of the nine patients marked side effects occurred consisting of water retention, sudden increase in weight, oedema, and in four patients a marked bradycardia developed. No changes in electroencephalograph recordings were noted during Cortisone administration.

(7) The results of the investigations lend no support to the claims that Cortisone given in high dosage for a relatively long period has any beneficial therapeutic effect in chronic schizophrenia.

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PHOTIC STIMULATION, IMAGERY, AND ALPHA RHYTHM

By

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PHOTIC stimulation, the exposure of the human eye to repetitive flashes of light, has been employed in recent years in three ways; as a diagnostic, as a therapeutic, and as a research method. In each case, its use has opened new frontiers of inquiry into the borderlands of neurology and psychology.

This paper presents certain observations which stem from the testing of exploratory hypotheses with regard to an expected relationship between photic stimulation and imagery, alpha rhythm, critical flicker frequency (CFF), personality test data, overt reactions, and after-images in three major diagnostic groups: schizophrenics, organic brain damage (paretics and others), and normal individuals (no history of brain damage or emotional disorder).

Since this is a report of exploratory work, no attempt has been made to apply rigorous statistical tests nor to arrive at final conclusions. The aim is rather to stimulate further research which may employ more adequate instruments, larger groups, or different conceptual schemes.

PREVIOUS RESEARCH

A large body of previous work exists which is relevant to the project at hand, however, only a few of the most pertinent articles will be noted here.

With reference to the imagery responses to photic stimulation, Grey Walter (33), (34) has described several subjective experiences to triggering where gross distortions in sensorium appear. In another article (32), he and others indicate that somatic, emotional, and mental changes can be induced by rhythmic sensory stimulation at appropriate frequencies. The kinds of responses to intermittent light have been described by Massucco (20) as (a) fragmentary (autoscopic) images of a geometrical nature, (b) more complete geometric figures (geometrizing response) often with colours,[†] and (c) in a very few persons, symbolic images consisting of concrete objects. The predominant response in fifty persons was the vividly coloured "geometrizing" image.

The colour response alone has been previously described, and is known as "flight of colours". The number of phases observed in the flight and its duration depend upon the intensity of the initial flash (8). It has been shown that as $\log I \times t$ of the flash varies arithmetically, both flight duration and the number of colour changes vary geometrically (2). The flight of colours phenomenon is considered as a special case of after-image. Mundy-Castle (22) in a case report states that vivid hallucinations were provoked by photic stimulation in a schizo-

* The work described here was undertaken in the Veterans Administration Hospital, Palo Alto, California. The facilities of the departments of neurology, psychiatry, and psychology were employed. The author wishes to express his thanks to the hospital administration and to Mr. Edward Dilkes, Dr. Fred Kamphoefner, Dr. Richard Worthington, Dr. Paul McReynolds, and Mr. Gideon Jean-Jacques for their assistance.

[†] It is interesting to note that D. O. Hebb, working at McGill, reports very similar coloured geometric images in response to the cutting off of visual stimulation for a period of hours. It may be worthwhile to speculate on the possibility of cortical free-wheeling in the two situations.

phrenic patient. It has also been found (14) that rhythmic stimulation acoustically or by tactile means, as well as visually, can produce neuromuscular activity or behaviour modification, including hypnotic-type stupors.

That imagery, in turn, is related to brain wave activity has been suggested. Walter (34) discusses imagery types as a kind of personality category and relates it to alpha activity. Some work does confirm such a relationship (25), (9) though without much consistency of findings.

Visual after-images have been found (13), in themselves, to be capable of depressing alpha rhythm in the occipital regions. This suggests that any association between supposedly enduring imagery types and characteristic brain waves must also consider the immediate impact of the image as a stimulus correlate disrupting alpha rhythm.

In reporting on the relationship between imagery and alpha characteristics, one investigator (9) speculates on the association between Rorschach response and the image-alpha complex. Some initial work, tying in Rorschach response with characteristic alpha, has been done (26), (4). In turn, Klein (16) finds that the kind of reaction to visual stimulation, namely the Phi phenomenon,* is associated with Rorschach responses. Since the Phi phenomenon is close to photic stimulation in some of its effects, one may expect to find further correlation of Rorschach scores with imagery. Similarly, there is evidence, summarized by R. Walter (31), which suggests that certain personality disturbances have particular or abnormal brain rhythms associated with them. From these findings, it may be expected that personality (as measured by psychological tests such as the Rorschach), imagery response to photic stimulation, and brain rhythms may eventually be describable in terms of consistent patterns or syndromes (24).

There is ample evidence that photic stimulation affects wave activity; especially in those persons with overt or incipient convulsive disorders (31, 7, 17, 23). However, some studies report that functional disorders also are associated with increased EEG responsiveness to photic stimulation (11, 28, 29). Such stimulation may produce behaviour disturbance including seizures and nausea (27).

Continuing the consideration of the response of brain-damaged patients versus those with functional disorders, there are several studies that report the critical flicker frequency† threshold of organic patients to be lower than that of schizophrenics (12, 35). In view of the dispute over the CFF response (21, 18, 1, 3, 5), especially as to whether the fusion phenomenon originates in the sensory cells or in the cerebral cortex, the reports of diagnostic group differences are important.

Several areas for exploration, expressed in question form, may be derived from the research cited:

- I. Can differences be expected in the amount and kinds of imagery response to photic stimulation of normals, brain-damaged and schizophrenic patients? (Differences in colour, geometric patterns, symbolic or meaningful objects, feeling states, observed movement, depth, or number of concepts).
- II. What changes in alpha rhythm will occur under photic stimulation in the three groups? (Normal, organic, schizophrenic).

* The Phi phenomenon is the impression of movement, the illusion, which a person experiences when a stationary stimulus is repeatedly exposed at a critical interval.

† CFF—the frequency per second at which a flickering light (repetitively flashing) is seen as a steady light.

- III. Are there characteristic images associated with increases in alpha amplitude or frequency (drive)?
- IV. What differences will be observed between organics and schizophrenics in their imagery responses that relate to CFFs?
- V. Will there be any association between performance on psychological tests and reported imagery?
- VI. Will a given stimulation rate produce identical imagery upon repetition?
- VII. What physical reactions will occur in response to photic stimulation?
- VIII. Is there any relationship between after-images and photic stimulation imagery in the three diagnostic groups?

SAMPLE

The population consisted of three groups: the normal group: eleven individuals with no history of brain damage or serious emotional disturbances; nine patients hospitalized with organic brain damage,* and twelve patients hospitalized with schizophrenia.†

APPARATUS AND MATERIALS

A Grass Model III EEG machine was employed; the photic stimulator was a 1951 Buffington 60 cycle AC oscillator with a stroboscopic light.

PROCEDURE

Subjects were seated with the light source two and one-half feet in front of them at eye level. Two occipital electrode replacements were made. The EEG record was run for several minutes and the alpha frequency established. The oscillator dial was then set for light firing at a frequency equivalent to the subject's observed alpha rhythm. This setting was termed "alpha equivalent".‡ The subject closed his eyes and the room was darkened. With manual control, one flash of light was fired and the subject asked what he had seen. This initial phase was the after-image report.

Following the after-image test, the stimulator was fired for 30 seconds at the alpha equivalent setting, and upon completion of stimulation, the subject was asked to relate what he had seen. Direct questions were then asked about patterns, colours, etc.§

In similar procedure, there followed three further runs; each for thirty seconds|| followed by a verbal report from the subject or patient. EEG records were run throughout all phases. The second phase employed a dial setting for stimulation frequency one-half the subject's initial alpha. The third phase was set for two times ($2\times$) alpha and the fourth phase was a repeat of phase one, the alpha equivalent setting. In addition, for the organics and schizophrenics,

* Diagnosis in this group were as follows: chronic brain syndrome associated with cerebral arteriosclerosis 1, hemiplegia (vascular origin) 1, psychosis with syphilitic-meningo-encephalitis (cerebral type) 1, chronic brain syndrome associated with brain trauma (penetrating gun-shot wound) 1, epilepsy, idiopathic and hereditary sclerosis 1, syphilis, tertiary, meningo-encephalitic type 1, epilepsy, grand mal, secondary to syphilis 1, syphilis, tertiary, CNS, tabo-paresis 1, chronic brain syndrome associated with CNS syphilis and epilepsy grand mal type 1.

† For the normals, the mean age was 31 with a range 21 to 40; for the schizophrenics, the mean age was 49 with a range 28 to 64; for the organics, the mean age was 57 with a range 31 to 72.

‡ The apparatus was inadequate and often did not fire at dial settings. Frequent misses or blanks occurred. The settings should not be taken too literally; the only certain designation is that of stimulation *per se*. The attempt, however, was to secure triggering or synchrony with the equipment at hand.

§ No obvious bias was apparent due to suggestion.

|| The stimulation duration of thirty seconds was based on recommendation of Dr. Charles Yeager, who reported that period adequate for the production of imagery response.

a fifth run was obtained where the speed of firing was gradually increased until either the subject reported flicker fusion had occurred, or until the apparatus reached its upper limits of flash frequency.*

During stimulation, subjects were observed for overt changes and these were recorded. In addition, the Rorschach and Kohs Block test had been administered to fifteen of the hospitalized patients. The test data were scored and recorded; EEG records were read and response data categorized and analysed.

RESULTS AND DISCUSSION

Table I presents an analysis of the kind and composition of images reported under photic stimulation for three diagnostic categories. In addition, Table I presents information on the number of separate images seen by each subject during the entire experiment. Although the number of subjects is too few to allow the application of tests of statistical significance, there are consistent differences among the groups. A common factor in many of the differences that appear in Table I is the greater productivity of the normal group, with the schizophrenic group second and the brain damage group least productive of responses.† The graduation of productivity holds true for colour, patterns, movement, and depth. It is reversed in the number of meaningful images, where the schizophrenic group is most responsive. The hallucinatory character of many of their responses is to be noted here.

The differences in the kinds of feeling state changes reported should be remarked upon. Emotional reactions along the pleasant-unpleasant continuum were most often found among the normals and never obtained from schizophrenics. Such findings are consistent with a defence-against-feeling description of that illness. One may speculate whether the loss of time sense reported by two normal subjects is, in any way, related to an hypnotic effect produced by photic stimulation. Such a loss is also found in hypnotic states.

Only one subject reported flicker sickness; yet four normals, one organic and eight schizophrenics reported a history of frequent adult motion sickness.

The changes in alpha rhythm are shown in Table I. In the normal group, the tendency is for a reduction in observable alpha; the reverse is more often true in both organic and schizophrenic groups where alpha becomes either more evident or where driving is seen.

TABLE II
Number of Distinct Images‡ per Subject for Entire Experiment

	Normals N=11	Organics N=9	Schizophrenics N=12
Number seeing:			
One image ..	0	2	5
Two images ..	2	6	2
Three images ..	4	1	3
Four images ..	3	0	1
Five images ..	0	0	0
Six images ..	1	0	0
Seven images ..	1	0	0
Mean=	3.7	1.9	2.5

* Once again, instrument difficulties arose. Its upper firing limit varied from 23 to 40 per second.

† Low productivity by brain-damaged patients is consistent with findings from psychological investigations. However, differences in age or intelligence may account for productivity variation in this experiment, for these variables were not controlled. Inspection of the few Weschler-Bellevue Intelligence Scale scores available for the patient group did not reveal any relationship in these groups between IQ and number of distinct image responses. Apathy, due to hospitalization itself, may also be a factor.

‡ A distinct image was defined as one idea, concept or response whole.

TABLE III
Image Reliability

	Normals	Organics	Schizophrenics
Same responses to first and second alpha equivalent runs	2	5	4
Different responses to first and second alpha equivalent runs ..	9	4	8

Reference to Table III indicates that a given rate of flicker does not necessarily produce the same response on two occasions. That it is more likely to do so among brain-damaged patients is a function of their low response productivity with consequent similarity of reaction to all flicker speeds. Because of the apparent dissimilarity of response to similar stimuli, it can be suggested that whatever mechanisms are involved in this imagery, some kind of a memory system operates.*

Table VI presents the available Rorschach scores compared with imagery response. Tests on more subjects would be required to elicit any trends.

TABLE IV
Rorschach Results and Imagery Responses

Organics			
	Imagery Movement	No Imagery Movement	
More than 2 Rorschach M†	1	1	
2 or less Rorschach M ..	2	1	
	More than 3 Colour Images	3 or less Colour Images	
Rorschach C‡ over 2 ..	0	2	
Rorschach C 2 or less ..	1	1	
Schizophrenics			
	Imagery Movement	No Imagery Movement	
More than 2 Rorschach M	2	0	
2 or less Rorschach M ..	5	3	
	More than 3 Colour Images	3 or less Colour Images	
Rorschach C over 2 ..	2	2	
Rorschach C 2 or under	0	2	
Totals			
	Imagery Movement	No Imagery Movement	
More than 2 Rorschach M	3	1	
2 or less Rorschach M ..	7	4	
	More than 3 Colour Images	3 or less Colour Images	
Rorschach C over 2 ..	2	4	
Rorschach C 2 or under	1	3	

Table V presents information on the CFF and imagery. From these data, it appears that even after subjects report light fusion, changes in imagery continue. If this can be verified, it would strengthen the interpretation of CFF phenomenon as a predominantly cortical function since images could not be experiences unless some flash discrimination, however subliminal, was taking place in the CNS. The present findings are in agreement with Irvine's (12),

* Retests on four patients after six months showed much similarity in the types of response, but some changes in descriptive wording.

† Human movement response.

‡ An index of the use of colour responses.

TABLE V
CFF Reactions in Organics and Schizophrenics

	Organics	Schizophrenics
Fusion point (CFF) achieved with imagery responses continuing*	4	3
No CFF achieved no further imagery	2	1
CFF not achieved†	2	8
Total‡	8	12

showing brain-damaged patients to have a lower level of CFF than reactive schizophrenics.

In Table VI is found an analysis of the similarity between after-image and photic stimulation response during the first alpha equivalent run. Once again, the findings show normal subjects more likely to produce radically different responses than are the hospitalized groups. In this case, there is no

TABLE VI
Common Elements in After Image (single flash) and Response to Photic Stimulation (repetitive flashes)

	After-image and photic S response identical (all elements in common)	Partial Identity of After-image and photic S response (some common elements)	No elements in common
Normals	0	8	3
Organics	5	4	—
Schizophrenics	5	6	1

instance of the normals having identical photic stimulation responses and after-images, whereas over half the organic group show identical response. The productions of schizophrenics resemble those of the organic patients more closely than those of the normal group.

Inspection of the records fails to reveal any particular kind of imagery associated with diminishing alpha or alpha drive. There seem to be no characteristic images (patterns, colours, etc.) which consistently occur when alpha rhythm changes occur; nor are there necessarily changes in alpha rhythm when a change in imagery is reported.

Inspection of the Kohs Block test scores available on nine patients does not reveal any relationship between scores on block pattern building and the number of patterns seen under photic stimulation.

Analysis of the Rorschach protocols, in comparison with the content of the photic images, reveals no similarity. In no case where Rorschachs were available was there reported a photic image which corresponded to the content of a Rorschach response.

Although the number of brain-damaged patients with focal as opposed to diffuse brain pathology was too small to allow any systematic comparison, initial comparisons show no major differences in response characteristics between the two groups.

With these observations in mind, it is possible to offer some remarks. Normals, schizophrenics, and brain-damaged persons apparently can be differentiated by means of photic stimulation. In their imagery, each group differs from the other, primarily in productivity but also in meaningfulness of

* Questionable, due to instrument failures. † Due to instrument inadequacies.

‡ One patient in the organic group was not tested.

the images and in the kinds of feeling states reported. It is easier to distinguish organics from schizophrenics and normals than to distinguish these latter two groups from one another with respect to imagery.

This does not hold true when the changes in brain rhythms under photic stimulation are examined. In this instance, the organics and schizophrenics seem more similar and the normals more distinctly apart from both. Demonstrable pathology may account for the records of organic patients; no such pathology has yet been found in schizophrenics. Nevertheless, both groups differ from normals not only in the production of imagery but in brain rhythm response to stimulation. In both patient groups, the observed responses are consistent with a state of reduced responsiveness to outer stimuli. In both cases, the symptoms and the underlying mechanisms may be interpreted as a lessened ability to respond adequately to the world outside. In both cases, EEG records may reflect this when the alpha fails to diminish under stimulation. Instead, in the schizophrenic group, there is alpha drive. This drive has been noted by Walter (34) to be associated with distorted sensorium. In the schizophrenic, the distorted sensorium regularly occurs. When it is considered that, in the schizophrenic, outer stimuli are not responded to, one may infer that the distortions involve a kind of cortical free-wheeling. It is even possible to suggest that a breakdown in the reticular "excitatory" centre or its pathways, as discussed by Magoun and his colleagues (6), might account for such a series of events. Thus, reduced sensitivity and inadequate capacity for response may be part of the same diencephalic mechanism.

Such an account is not inconsistent with EEG studies (10, 19) or with the ordinary behaviour of these patients.

SUMMARY

A preliminary study has examined the responses to photic stimulation of normals, organics and brain-damaged schizophrenic patients. Consistent differences in the productivity of patterns, colours, depth and movement were found. Special differences in the meaningfulness of images were noted. Examination of EEG records indicates that schizophrenics are like organics in their responses and that the responses of both groups are consistent with a theory of reduced sensitivity and response capacity, perhaps due to diencephalic dysfunction. No relationships were found among reported images and psychological test data.

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METABOLIC VARIATIONS IN MANIC-DEPRESSIVE PSYCHOSIS

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IN previous investigations of changes observed in the blood levels of acetyl-methylcarbinol and butane-2:3-diol in patients with manic-depressive psychosis (Dawson *et al.*, 1954), the blood levels of a large number of patients in one mood phase were compared with the levels in another group of patients in a different mood phase. This procedure showed that the differences between the various mood phases were statistically significant. A lack of correlation in time between the chemical changes and the alteration in mood might account for the limited degree of correlation obtained. Thus, if the chemical change preceded the mood change, some of the data would not correspond with the observed mood state during which the blood sample was taken.

Another uncontrolled factor in the previous investigation was the diet; whilst all the blood samples were taken after a 12 hour fast, there was a large difference in the previous dietary history of the patients due to their mental state. Again, only blood levels were investigated and these might have been considerably affected by alterations in kidney activity.

For all these reasons, a different approach to the problem was made, and a small number of patients has been studied closely through a series of mood changes so as to enable us to determine the time relationship, if any, between the change in mental state and the chemical change. The patients were segregated into a small ward where their food intake was determined and 24-hour urine collections made; whilst in the unit, patients were maintained without sedation and without electroconvulsant therapy.

On the basis of the previous work, it was concluded that the variations observed in the blood levels of acetylmethylcarbinol and butane-2:3-diol did not, in themselves, determine a change in mood but were indicators of some other, more fundamental alteration in the metabolic state of the subject. Consequently, changes in extracellular fluid volume as estimated by determinations of the thiocyanate space, were also investigated with these patients. Estimations of urinary constituents were also made to determine the effect of the kidneys in influencing blood levels.

ORGANIZATION OF THE WARD

This consisted of a dormitory with accommodation for 4 patients, a room for nursing staff, an office for the psychiatrist and a day room in which the patients could read, listen to the wireless or do handicrafts. Two special nurses

were appointed to the unit, with a third who acted as relief during the days when the permanent staff was off-duty. The unit nurses were responsible for the ward from 6 a.m. to 10 p.m. and kept careful, detailed notes on the behaviour and affect of all patients in the ward; they also attended to the patients' meals, weighing the food provided and any left, measuring the fluid intake and supervising, as far as possible, the collection of 24-hour samples of urine. During the night, the research unit was supervised by the nursing staff on duty in the admission hospital, of which it was a part.

Patients were weighed twice a week. The special diet, selected to provide an intake of approximately 2,400 calories, was supplied from the main kitchens; it was not difficult to prevent the patients from obtaining additional food, as the unit was separated from the rest of the hospital.

SELECTION OF PATIENTS

The ideal patient for this investigation should be a young adult (under 40), of average intelligence exhibiting alternating manic and depressive mood changes, with intermittent normal periods, and showing minimal personality or intellectual deterioration. Such cases are rare today in the mental hospital ward and to supplement our clinical material, older patients were included who had shown spontaneous remission from previous manic or depressive episodes. The criteria for selection in this group were (*a*) no evidence of marked deterioration in intellect or personality, (*b*) a reliable history of more than one previous attack of mania or depression of relatively short duration with remission without the use of electroconvulsant therapy, (*c*) the occurrence of the first attack of mania or depression before the involutional period. The inclusion of this type of patient has given us data on some individuals who remained in the same mental state throughout the investigation; these data are reported to demonstrate that no significant chemical change occurs during the unaltered mood state.

PSYCHIATRIC ASSESSMENT

A full psychiatric history was obtained, where possible, from the patient and near-relatives. Psychological testing was used to augment clinical estimation of general intelligence and to compile a personality profile of each patient. The mood change, whilst the patient was in the unit, was determined by reference to a daily clinical assessment by the psychiatrist, and a detailed nursing report on the activities and behaviour of each patient. In order to delineate minor fluctuations of mood and to try to forecast the appearance of overt mood changes, this was supplemented by a monthly routine Rorschach test.

COLLECTION OF MATERIAL FOR CHEMICAL ANALYSIS

Blood samples (10–15 ml.) were obtained twice weekly from fasting patients for the determination of acetylmethylcarbinol (AMC), butane-2:3-diol (BD), glucose and pyruvate. Thiocyanate space determinations were made weekly.

Twenty-four hour collections of urine were made as a routine procedure and analysed every other day for AMC, BD, creatinine and uric acid.

METHODS

AMC and BD were determined by the method of Happold and Spencer (1952) adapted for blood by Dawson, Hullin and Pool (1954). Similar methods were used for the urine analysis, the protein precipitation stage being omitted. Blood glucose was estimated by the method of Hagedorn and Jensen (see Hawk

TABLE I

Variations in the Blood Levels of Glucose, Pyruvate, Acetylmethylcarbinol (AMC), Butane-2:3-diol (BD) and in the Thiocyanate Space (TS) of Subjects With and Without Mood Changes
Blood Levels are Recorded as mg. 100 ml. $\pm$ Standard Error of the Mean; Thiocyanate as litres/Kg. Body Weight

Subject No. of Blood Determinations	Mood	Glucose	Pyruvate	AMC	BD	BD/AMC	AMC + BD	No. of T.S. Determinations	T.S.
Patients without mood changes:									
J.H. ..	14 Normal	80 ± 1.7	0.78 ± 0.02	0.031 ± 0.004	0.323 ± 0.018	15.1 ± 3.3	0.354	7	0.293 ± 0.008
A.R. ..	12 Normal	87 ± 2.0	0.83 ± 0.05	0.034 ± 0.006	0.305 ± 0.011	12.8 ± 3.1	0.339	7	0.309 ± 0.010
G.J. ..	40 Mania	80 ± 1.0	0.82 ± 0.05	0.034 ± 0.003	0.314 ± 0.019	13.0 ± 1.6	0.348	20	0.305 ± 0.005
H.H. ..	16 Depression	83 ± 1.3	0.81 ± 0.05	0.039 ± 0.003	0.259 ± 0.020	8.0 ± 1.2	0.298	6	0.282 ± 0.008
Patients with mood changes:									
H.A. ..	37	81 ± 1.0	0.98 ± 0.01	0.037 ± 0.008	0.411 ± 0.040	21 ± 2.1	0.448	18	0.385 ± 0.013
C.B. ..	33	79 ± 1.0	1.05 ± 0.12	0.030 ± 0.006	0.300 ± 0.028	18 ± 2.4	0.330	15	0.356 ± 0.017
W.S. ..	17	75 ± 1.5	0.81 ± 0.03	0.026 ± 0.005	0.403 ± 0.034	18 ± 3.4	0.429	9	0.337 ± 0.014
F.K. ..	13	90 ± 2.5	0.89 ± 0.04	0.050 ± 0.008	0.214 ± 0.021	8.5 ± 2.2	0.264	7	0.300 ± 0.014

et al., 1947), and pyruvate by the method of Friedemann and Haugen (1943). Thiocyanate space determinations were made using the method of Lavietes *et al.* (1936), the correction for red-cell thiocyanate being omitted. The actual serum thiocyanate estimations were made by the method of Bowler (1944).

Uric acid in urine was determined by the method of Benedict and Franke (1922) whilst urinary creatinine was estimated by the modification of the Jaffe colour reaction suggested by Folin and Wu (1919).

RESULTS

Table I has been constructed by dividing the patients into two groups; those patients whose mood remained constant during the whole of the period studied and those who had mood swings whilst being investigated. If the latter group showed a larger standard error of the mean of the various chemical determinations for the whole period of investigation then it could be inferred that a greater variation exists in patients suffering from mood changes. Only in the results for thiocyanate space and butane-2:3-diol, does a larger coefficient of variation exist in the group with mood swings. This variation is probably reduced by the small period of time relative to the total period under study during which the actual mood change was operating.

As the table shows, there is no large difference between any of the mean values for the group with mood changes compared with the group of patients with constant mood. It may be concluded from this treatment of the data that, if any chemical change occurs, it persists only for a relatively short time in relation to the change in mood. The exception may be that of thiocyanate space which does vary more in mood swingers than in the group with constant mood.

Similar treatment of the results of urine determinations (Table II) did not show a larger variation in the group with mood changes and provided no evidence to support the view that a change in mood is associated with any variation in the urinary excretion of AMC or BD.

TABLE II
Variations in the 24-Hour Urinary Excretion of AMC, BD and Uric Acid of Subjects With and Without Mood Changes. (Units: mg./g. Creatinine $\pm$ S.E.M.)

Subject	No. of Deter- mina- tions	Mood	AMC		BD		Uric Acid	
			Creatinine		Creatinine		Creatinine	

(a) Patients without mood change:

J.H.	..	14	Normal	..	1.18 ± 0.11	8.6 ± 0.65	180 ± 4
A.R.	..	19	Normal	..	0.82 ± 0.07	11.4 ± 1.00	230 ± 10
G.J.	..	52	Mania	..	2.60 ± 0.22	17.1 ± 0.80	160 ± 24
H.H.	..	18	Depression	..	1.06 ± 0.02	10.9 ± 0.47	190 ± 8

(b) Patients with mood changes:

H.A.	..	50			0.71 ± 0.06	9.2 ± 0.48	246 ± 7.4
C.B.	..	53			0.71 ± 0.05	10.3 ± 0.53	232 ± 5.4
W.S.	..	21			1.03 ± 0.10	8.4 ± 0.41	184 ± 4.8
F.K.	..	12			0.59 ± 0.05	7.45 ± 0.50	189 ± 11.5

The results for patients showing changes of mood are next classified into the depressed, manic or normal interphases in order to see whether any change

TABLE III

Variations in Blood Levels of Glucose, Pyruvate, AMC, BD and Thiocyanate Space (T.S.) of Subjects During the Normal, Depressed and Manic Phases of Manic-depressive Psychosis. (Units as in Table I)

Subject	No. of Blood Determinations	Glucose	Pyruvate	AMC	BD	BD/AMC	AMC+BD	No. of T.S. Determinations	T.S.	T.S. (litres)
Normal phases:										
H.A.	9	82±2.3	0.84±0.12	0.028±0.007	0.298±0.028	24.8±5.0	0.326	5	0.445±0.032	22.9±2.3
C.B.	15	79±1.4	0.97±0.05	0.028±0.007	0.267±0.023	18.1±3.6	0.295	7	0.417±0.023	26.6±1.9
W.S.	13	74±1.4	0.80±0.04	0.033±0.005	0.417±0.037	11 ±1.4	0.450	7	0.327±0.016	23.6±1.1
F.K.	6	88±4.2	0.84±0.02	0.049±0.009	0.200±0.025	6 ±2.5	0.249	3	0.32	21.5
Manic phases:										
H.A.	15	78±1.4	0.98±0.07	0.036±0.008	0.541±0.065	21.3±2.8	0.577	7	0.342±0.018	15.7±0.8
C.B.	17	76±1.2	0.80±0.04	0.016±0.001	0.363±0.037	23.4±4.2	0.379	6	0.311±0.012	20.9±0.7
W.S.	4	74±2.9	0.73±0.07	0.010±0.00	0.391±0.064	38 ±6.6	0.401	2	0.287	20.8±0.2
F.K.	2	101	1.06	0.074	0.172	3.5	0.246	1	0.27	17.3
Depressed phases:										
H.A.	15	83±1.4	0.99±0.07	0.047±0.021	0.277±0.033	16.3±3.2	0.324	7	0.393±0.003	17.8±0.1
C.B.	7	84±3.7	1.71±0.55	0.069±0.025	0.304±0.087	11 ±3.8	0.373*	2	0.302	19.6
F.K.	5	90±2.9	0.87±0.06	0.026±0.005	0.274±0.030	13 ±4.1	0.300	3	0.290	18.1±0.5

The test of significance adopted was the analysis of variance; the following results were obtained when the thiocyanate space values for the different mood phases were treated in this way.

H.A.: Between normal, manic and depressed phases. Probability that difference due to random variation $p < 0.05$.

C.B.: Between normal and manic phases. $p < 0.01$.

W.S.: Between normal and manic phases. $p < 0.05$.

F.K.: Number of estimations in different phases was too small for satisfactory statistical analysis.

takes place in the chemical constituents of the blood in the various mood states. It is assumed in this treatment that any chemical change is closely associated in time with the mood state.

The results, shown in Table III, demonstrate that the thiocyanate space, either as an absolute determination or as a fraction of the body weight, is at a maximum during the normal interphases. The mean thiocyanate space values during mania are not significantly different from those in depression.

Patient W.S., the only one of the group to have only one short mood change, shows a significant difference between the blood AMC level in mania and normality and consequently is the only patient in the group whose blood BD/AMC ratio is significantly increased in mania. In contrast, patient F.K. who had a series of rapid fluctuations in mood, shows the opposite of this change in mania. The other two patients, H.A. and C.B., who had long periods of either mania or depression with relatively long periods of normal mood, do not show any very significant chemical change.

This method of treatment of the data assumes that, if the mood change persists, so must any chemical change, and does not allow of the possibility that the chemical changes might be out of step with the mood changes. The results in Table III indicate that the thiocyanate space alterations are associated in time with the changes of mood. The changes in urinary excretion of AMC, BD and uric acid associated with the mood of the patient are shown in Table IV.

TABLE IV

Variations in the 24-Hour Urinary Excretion of AMC, BD, and Uric Acid of Subjects During the Normal, Depressed and Manic Phases of Manic-depressive Psychosis (mg./g. Creatinine)

Subject			No. of Estimations	AMC Creatinine	BD Creatinine	Uric Acid Creatinine
Normal phases:						
H.A.	..	..	12	0.8 ±0.20	12.8±2.1	260± 6
C.B.	..	..	19	0.6 ±0.05	10.4±0.8	230± 5
W.S.	..	..	13	1.24±0.14	8.3±0.5	180± 6
F.K.	..	..	6	0.75±0.10	7.3±0.97	190±17
Manic phases:						
H.A.	..	..	24	1.1 ±0.20	9.3±1.8	240±14
C.B.	..	..	26	0.8±0.10	9.0±0.4	260± 7
W.S.	..	..	6	0.5±0.12	8.4±0.7	190± 7
F.K.	..	..	1	0.5	6.9	140
Depressed phases:						
H.A.	..	..	21	0.5±0.05	7.7±0.4	240± 6
C.B.	..	..	12	0.6±0.04	13.6±2.2	190±10
F.K.	..	..	6	0.42±0.02	7.7±1.4	170±14

The excretions are expressed as a ratio of creatinine excretion to minimize the error due to urine loss, assuming that the creatinine excretion would be approximately constant from day to day. No clear picture emerges of specific differences in the excretory pattern between the various mood states.

The data has been examined so far on the assumption that any chemical changes are associated simultaneously with the mood changes and that they

persist as long as the mood change persists. This is true for thiocyanate space but not for the other chemical estimations which have been made. The next development was to consider the possibility that the chemical change precedes the mood change and does not persist for the whole period of the altered mood. The group of patients studied could be subdivided on the basis of the periodicity of mood changes. Two patients (H.A. and C.B.) had long periods of mania and depression with relatively long, normal interphases ("slow-swingers") whilst the other two (F.K. and W.S.) had only short periods of mania and depression with limited normal interphases. It might well be that the periodicity of the chemical changes was likewise different in the two sub-groups. On empirical grounds, we assumed that in cases of short periodicity the chemical changes preceded the mood changes by 1 week whilst in the two patients with more infrequent changes the time interval between chemical and mood changes was $3\frac{1}{2}$ weeks. The results were then re-grouped on this assumption by moving the time scale with respect to the chemical data so that every mood change was located either 1 or $3\frac{1}{2}$ weeks before it actually occurred. Subject to this change, the results were again classified according to the various mood states (Table V). Thiocyanate space values were not treated in this way since the change in this factor actually corresponds in time with the mood change and does not so correspond if the time scale is moved.

TABLE V

Variations in the Mean Blood Level Values of Glucose, Pyruvate, AMC and BD in Cases of Manic-depressive Psychosis for the Period (a) 3.5 Weeks, (b) 1 Week Preceding the Onset of the Mood Phase to the Corresponding Time Before the End of the Phase. (Units as in Tables I and III)

Subject	No. of Estimations	Glucose	Pyruvate	AMC	BD	BD/AMC	AMC+BD
Normal phases:							
(a) H.A.	9	78.5	0.86	0.034	0.465	15.4	0.499
(a) C.B.	11	80.6	1.00	0.029	0.237	11.4	0.266
(b) W.S.	14	76	0.82	0.045	0.391	15.6	0.436
(b) F.K.	4	97	0.96	0.067	0.174	3.5	0.241
Manic phases:							
(a) H.A.	7	81.3	0.99	0.013	0.345	32.3	0.358
(a) C.B.	12	78.7	0.87	0.016	0.317	27	0.333
(b) W.S.	4	77	0.72	0.023	0.372	24.3	0.395
(b) F.K.	2	95.5	0.97	0.015	0.266	20.5	0.281
Depressed phases:							
(a) H.A.	14	81.5	1.08	0.040	0.484	18.8	0.524
(b) F.K.	5	85.4	0.81	0.048	0.208	7	0.256

The data was treated by the analysis of variance. The probability that the decreased AMC blood level in the manic phases was due to random variation was <0.01 for patient H.A. and <0.05 for patients C.B., W.S. and F.K.

Considering the greater BD/AMC ratio of the manic phases in a similar manner gave values of $p < 0.01$ for patients H.A., C.B. and <0.05 for patients F.K. and W.S.

The re-arranged results demonstrate that, in the manic phase, the AMC blood level is significantly lower in every case than in the normal phase;

corresponding to this, the blood BD/AMC ratio is also increased in the manic phase. The results during depression would seem to indicate that the AMC values are not significantly different from normal values. The BD values show no consistent change between the mood states; similarly, neither the blood glucose nor pyruvate levels show any consistent alteration.

The urinary excretions treated in the same way are presented in Table VI.

TABLE VI

Variations in the Mean 24-Hour Urinary Excretion of AMC, BD, and Uric Acid in Cases of Manic-depressive Psychosis. The Data Tabulated under any Mood State Include Results Obtained During the Period (a) 3.5 Weeks, (b) 1 Week Preceding the Onset of the Mood Phase but not those During the Corresponding Time Interval at the End of the Phase. (Units: mg. per g. Creatinine)

Subject				No. of Estimations	AMC Creatinine	BD Creatinine	Uric Acid Creatinine
Normal phases:							
(a)	H.A.	..	..	15	0.95	9.2	276
(a)	C.B.	..	..	19	0.80	10.5	248
(b)	W.S.	..	..	16	1.07	8.2	188
(b)	F.K.	..	..	3	0.77	8.6	193
Manic phases:							
(a)	H.A.	..	..	9	0.38	7.4	231
(a)	C.B.	..	..	26	0.61	10.7	222
(b)	W.S.	..	..	4	0.92	9.1	170
(b)	F.K.	..	..	3	0.40	7.4	176
Depressed phases:							
(a)	H.A.	..	..	25	0.74	9.85	226
(b)	F.K.	..	..	5	0.40	6.5	168

The test of significance was the analysis of variance. The probability that the decrease in uric acid/creatinine values observed in both the manic and depressed phases might be due to random variation was <0.01 for patient H.A., and <0.05 for patients C.B. and W.S. The small number of determinations obtained in each phase for patient F.K. did not permit satisfactory statistical analysis.

There is a marked fall in the urinary AMC excretion during the manic phase; this is associated with a decreased blood level so the altered urinary excretion is not responsible for the altered blood level but is probably caused by it. The AMC excretion is also reduced in depression.

There is no consistent alteration in the BD excretion pattern but the uric acid/creatinine ratio is reduced both in mania and depression. These observations could not be discerned from the urine results when treated on the assumption that the chemical and mood changes occur simultaneously.

DISCUSSION

Previous work by Dawson *et al.* (1954) has shown that the blood AMC level is reduced below normal in the manic phase. This conclusion emerged from a statistical study of results derived from a large number of subjects from whom only one or two blood samples were taken. The observation could not be demonstrated in every individual case and there was quite a large degree of variation in the extent of the reduction. It was possible that the variation might be due to a lack of correlation in time between the mood state and the blood level of AMC. In this series of patients, we have been able to demonstrate that the

blood changes are not simultaneous with the mood changes but occur prior to them. The period between the alteration in blood values and mood change varies from subject to subject and appears to be related to the pattern of mood variation.

The two patients with long periods of mania, depression and normality (the so-called "slow-swingers") seem to exhibit a change in blood level from 3-4 weeks before the mood change is observed. In these patients the chemical change has to persist for quite a long period before the mood state changes. There is little evidence that the magnitude of the blood change determines the length of time it has to operate before the onset of mood alteration.

Statistically there does not appear to be any characteristic alteration in blood AMC level in depression as compared with that in the normal interphases. This may, in part, be due to the difficulty of accurately timing the onset of mood change, particularly in the "slow-swingers". Our general impression is that the blood AMC level is increased at the beginning of a depressed phase but it is very difficult in some of these patients to determine exactly when depression ends and normality begins.

The blood BD levels do not indicate any specific effect and may be regarded as resulting from non-specific reduction of the AMC. Since the BD levels do not vary significantly, the BD/AMC ratio is markedly increased prior to and during the early part of a manic phase.

The clearance rates of AMC and BD by the kidney indicate that 95 per cent. of these compounds filtered in the glomerular filtrate are re-absorbed by the renal tubules, suggesting that when the blood level falls AMC excretion in the urine will be decreased. This reduced excretion of AMC has been demonstrated so it is unlikely that the kidney is responsible for the reduction in blood level observed. The blood level of BD prior to and during the initial part of a manic attack is not so clearly altered and the BD urinary excretion values for this period are correspondingly variable.

Pyruvate is the immediate precursor of AMC and Dawson and Hullin (1954) showed that pyruvate, when injected, will increase the AMC blood level. In the patients studied however, alterations of blood pyruvate level seem to play no part in producing the variations in AMC level; neither is the latter determined by the blood glucose level. This is in spite of the demonstration in the earlier communication (Dawson *et al.*, 1954) that the blood AMC level is different during the absorptive phase of digestion from that in the fasting state.

The thiocyanate space determinations in subjects with constant mood do give relatively constant values. The values for fluid in this space as a percentage of the total body weight are high when compared with the results of other workers, largely due to the omission of the correction for the thiocyanate which has entered the red blood cells. This simplification of the procedure does not however invalidate the finding of a marked reduction in thiocyanate space associated with the manic and depressed phases, the change not occurring before the mood change. The observed reductions are towards values which are more nearly normal for the body weight and sex and it is during the mentally normal interphases that the most abnormal values for thiocyanate space are found. The changes observed may be due to a true increase in the extracellular fluid volume or to an alteration in the permeability of cells with respect to the thiocyanate ion. Further work is necessary to decide which of these two mechanisms is operating to produce the increase in thiocyanate space seen in the normal interphases.

The urinary uric acid/creatinine ratio is reduced in both mania and

depression. This reduction can only be shown when the same slipped time scale is used as is used for the correlation of blood AMC level with mood state. If the ratio can be taken as an index of adrenal cortical activity, then there is reduced activity of this endocrine organ prior to the onset of a manic or depressed phase as compared with that preceding a normal phase.

It is interesting to speculate that the chemical changes we have observed might in fact be produced by alterations in activity of the adrenal cortex. There is no evidence that the reduced AMC blood level will itself produce a mood change. Similarly it is difficult to understand how the abnormally large thiocyanate space could be responsible for the production of a normal interphase. However, it does seem possible that an alteration in adrenal cortical activity could be responsible both for the chemical changes and, in susceptible subjects, for the disturbance of affect.

Further work is proceeding to evaluate the biochemical significance of electroconvulsant therapy in the treatment of disturbances of affect (with reference to any possible correlation between chemical change and the achievement of a more stable mood state with treatment). Additional investigations are necessary in order to implicate the adrenal cortex in the pathogenesis of mania and depression and the associated changes in blood AMC and thiocyanate space.

ACKNOWLEDGMENTS

It is a pleasure to acknowledge the technical assistance of Mrs. Beryl Taylor and the invaluable help of the nursing staff in charge of the patients in the research unit at Menston Hospital, particularly Messrs. McKinley, Ryder, Crookes and Matthews.

Our thanks are also due to the Menston Hospital Management Committee both for financial assistance and for providing the facilities.

SUMMARY

(1) The blood levels of acetylmethylcarbinol, butane-2:3-diol, pyruvate and glucose have been determined at twice-weekly intervals in a group of patients exhibiting alternating manic and depressive mood changes and in a group of subjects without mood variation while under observation. In addition, the thiocyanate space and 24-hour urinary excretions of acetylmethylcarbinol, butane-2:3-diol, uric acid, and creatinine have also been estimated at frequent intervals.

(2) An increase in the thiocyanate space is associated with the normal inter-phases in the group showing alternating manic and depressive mood changes. The variation in thiocyanate space in the group without a mood change during the period of investigation is within normal limits.

(3) A decrease in both the blood level and urinary excretion of acetylmethylcarbinol precedes and is associated with the early part of a manic phase. The relationship in time between the chemical change and the mood change is determined by the periodicity of the cycle.

(4) The uric acid/creatinine ratio is decreased before and in association with the initial part of both manic and depressed phases.

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IRON AND CALCIUM IN STURGE-WEBER DISEASE

By

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THIS is a report of the chemical analysis of iron and calcium in the brains of three cases of Sturge-Weber disease. Although the clinical and pathological features of this syndrome have been well described, the chemistry of the characteristic deposits is less well understood, and there is a conflict of opinion as to whether iron is present in increased amount.

Owing to the kind co-operation of Mr. Alexander of the Neurosurgical Unit, Frenchay Hospital, it has been possible to re-investigate this problem using material derived from lobectomy specimens. The material had been stored in formol saline for some months before the analysis was carried out.

Microscopic examination showed the usual picture of meningeal angioma and massive mineral deposits in the outer part of the affected grey matter. There were also a few concretions lying more deeply in the white matter in all the specimens (Dr. R. M. Norman).

PRIOR LITERATURE

Chemical assessment of the iron and calcium in the cortex has been made in cases of this type by Eaves (1926) and by Wachsmuth and Löwenthal (1952). Eaves found a very large excess of total iron in a case preserved in formol; whereas Wachsmuth and Löwenthal, in fresh material, found no excess—the latter authors showed that preservation in formol raised the iron content but not to a level anything approaching that found by Eaves. All these authors found a large excess of total calcium. It should be noted that the iron estimated by these authors will include that due to the blood. Also that they did not assess the inorganic or readily available iron, which would have been increased in the case of Sturge-Weber disease if there had been a conversion of part of the organically bound iron to the inorganic form.

METHODS

“Inorganic” iron was estimated by the method of Tompsett (1935) and “Total” iron (i.e. all the iron except that due to the bound iron of the blood) by the method of Tingey (1937).

Total calcium was estimated by ashing and precipitation of the calcium from an HCl solution of the ash by saturated ammonium oxalate in the presence of a sodium acetate buffer at pH 5.0—the oxalate precipitate was re-dissolved in hot dilute H_2SO_4 and the liberated oxalic acid titrated against KMnO_4 .

RESULTS

It will be seen from Table I that no excess of inorganic or total iron, over the control specimens preserved in formol, was found, either in the cortex or white matter.

TABLE I
(Number of cases in brackets)

Cortex mg./100 m. Wet Tissue	"Inorganic" <i>Fe</i>	Total	Ca Total
Control fresh	1.28 (10)	2.99 (6)	6.60 (1)
Control formol	3.24 (5)	5.51 (5)	13.60 (5)
Case 1	2.27	4.30	10,824
Case 2	1.18	3.85	1,660
Case 3	3.37	5.75	490
White matter:			
Control fresh	1.23 (9)	2.59 (6)	8.00 (1)
Control formol	3.12 (3)	4.96 (5)	9.33 (5)
Case 1	1.20	1.80	156
Case 2	2.67	4.52	171
Case 3	3.35	5.80	110

TABLE II

Cortex mg./100 gm. Wet tissue	Ca	P	Ca in Excess of $\text{Ca}_3(\text{Po}_4)_2$
Calcified nodule hot acetic acid ..	10,500	3,800	8,600
Calcified nodule hot saline ..	220		
Homogeneous paste hot acetic acid	1,695	137	1,430
Homogeneous paste hot saline ..	149		

A large excess of total calcium as compared with the formal controls was found, both in the cortex and in the white matter, but especially in the cortex.

FORMS OF CALCIUM

A rough assessment of the way in which the calcium was combined was made by doing parallel calcium and phosphorus estimations on (1) a calcified nodule and (2) a homogeneous paste of the affected cortex. The material was boiled with 30 per cent. acetic acid in which calcium phosphate is soluble, and with dilute saline in which calcium oxide and sulphate are soluble.

It will be seen from Table II that there is more Ca than can be accounted for as $\text{Ca}_3(\text{Po}_4)_2$ —this excess of Ca is probably largely CaCO_3 , as the nodule evolved gas with N/10 HCl.

It would appear that in the calcified nodule about 220 mg. of the 10,500 mg. total Ca in 100 gm. cortex is water soluble, and therefore probably CaO or CaSO_4 ; and that at least 8,380 mg. is due to CaCO_3 .

The Ca due to $\text{Ca}_3(\text{Po}_4)_2$ will be less than 1,900 mg. according to the amount of other P salts present.

A higher percentage of water soluble calcium salts was present in the homogeneous paste.

DISCUSSION

There would seem to be no doubt as to the enormous amount of calcium present in these cases, and that this element is present in excess in the white matter as well as in the cortex.

In these cases no excess of iron was found, thus confirming the findings of Wachsmuth and Löwenthal.

In the case reported by Eaves, there seems a possibility that she assessed some salts other than an iron salt. She did not estimate the iron as such, but weighed the insoluble residue remaining after extraction with hot concentrated acetic acid, and assumed that this was due to $\text{Fe}_3(\text{PO}_4)_2$.

It is curious that the mineral deposits give a positive Prussian Blue reactive histologically in these cases. The deposits are evidently not due to a conversion of organic to inorganic Fe in the tissue by pathological means. It would seem possible that the calcium deposits act as an adsorbent for readily available iron normally present in the tissue.

SUMMARY

The cortex and white matter of the brain in three cases of Sturge-Weber disease contained no excess of inorganic or total iron, although iron was demonstrable by histological means.

These contained a large excess of calcium, mostly as phosphate and carbonate.

The author wishes to thank Dr. R. M. Norman for his helpful interest in this investigation.

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Clinical Studies on α (2-Piperidyl) Benzhydrol Hydrochloride, a New Antidepressant Drug

1. The pharmacology of a new antidepressant drug, Meratran, is reviewed briefly.
2. Clinical trial in 320 cases disclosed that the therapeutic indications of this compound are roughly similar to those of the amphetamines.
3. Reactive depressions responded effectively in 90 per cent. of the author's relatively small series.
4. Endogenous depressions responded favorably in 65 per cent. of the author's cases.
5. The drug has proved valuable in office practice because the appetite loss and the cardiovascular pressor reactions sometimes observed after the administration of the amphetamines are not encountered. In addition, the drug seldom interferes with nocturnal sleep, and when it produces anxiety side reactions these are less severe and less disturbing subjectively than those encountered with the amphetamines.
6. When anxiety or agitation comprise a sizable proportion of the clinical picture the drug should be used with caution.
7. Preliminary observations indicate that the drug may have therapeutic usefulness, in addition to the depressive states, in some of the tics, in narcolepsy, and as an adjunct in the management of certain epileptics.
8. Effective dosage ranges (except in narcolepsy) vary between 3.0 and 25.0 mg. daily.
9. Wider clinical trial of this compound appears justified.

(Author's Abstr.)

* A number of abstracts in this section are reproduced from *Chemical Abstracts*. To the Editors of this Journal we extend our grateful thanks.

The Effect of Meratran on Twenty-five Institutionalized Mental Patients

A study was conducted on 25 institutionalized psychotic patients with chronic courses, selected because of their depressive and/or regressive symptoms.

Meratran was found to be a central nervous system stimulant useful in the field of psychiatry and with certain indications and contraindications: (1) indications: (a) schizophrenics without delusions having restriction of interest and activity and with depressant features, (b) psycho-motor retardation and/or blocking of communication, (c) long-term hospitalized schizophrenics with severe deterioration; (2) contraindications: (a) patients with delusions, (b) patients with anxiety, (c) disturbed patients with cerebral arteriosclerosis.

(Authors' Abstr.)

Stimulation of the Amygdaloid Nucleus in a Schizophrenic Patient

The patient's principal response with this stimulation was a reaction of rage appearing when the current approached an intensity of 5 ma. When the current was reduced to 4 ma., the rage disappeared and the patient was able to discuss it quite objectively. The rage returned each time that the current was increased to 5 ma. and similarly disappeared when the current was reduced to 4 ma. The patient states that she was perfectly aware of her feelings but described them as unusual for her. During the periods when the current was below threshold she was rather amused by her reaction. At various intervals repeat X-rays were obtained which indicated that the electrodes had not shifted. Despite this, on subsequent treatment utilizing the same parameters of stimulation, the patient developed intense fear with an impulse to run. The common feature was a strong emotional response.

(Authors' Abstr.)

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Experimental Psychiatry. II. Clinical and Physio-Chemical Observations in Experimental Psychosis

1. Experimental psychiatry, i.e. the comprehensive study of experimentally produced psychosis, is important for the advancement of psychiatry.
2. The diethylamide of d-lysergic acid (LSD) has proven an excellent tool for investigation of experimentally produced psychotic-like manifestations.
3. Clinical, psychological, physiological and biochemical evidence is offered which indicates that the adrenalin system is involved in the LSD-produced emotional and psychotic phenomena.
4. Theoretical reflections concerning the enzymatic adrenalin system as the basis of the development of schizophrenia and other psychoses are reported.

(Authors' Abstr.)

Chlorpromazine Treatment of Mental Disorders

Chlorpromazine has a diverse pharmacological action on the human organism. A considerable body of evidence has been accumulated pointing to its therapeutic efficacy in many kinds of mental disorders. It is a drug of low toxicity even in large doses and one which may be administered over long periods of time without an undesirable increase of tolerance.

It appears to be a highly effective agent for controlling psychomotor excitement of all kinds without the undesirable effects of the standard methods and maintaining the patient in a fairly accessible state at all times. Its action on other types of mental illness is not so remarkable but is certainly worthy of further investigation, particularly in the chronic schizophrenic patients in whom most treatments are unrewarding. Facilitation of communication together with a remarkable objectivity towards significant ideas and feelings has occurred in many of this group.

Speculation about the mode and site of action of the drug seems premature but such evidence as there is suggests that it is a subcortical one. While in the initial states of treatment there is a definite resemblance in the behavior of these patients to those who have been lobotomized there are none of the deficit found in the latter. Neither the dosage nor the mode of administration of the drug is in any way standardized. The initial results obtained in Europe and this country have been satisfactory enough to justify a thorough clinical investigation of chlorpromazine and a search for even more powerful related compounds.

(Author's Abstr.)

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Diagnostic Aspects of a Study of Intracellular Phosphorylations in Schizophrenia

1. This test affords a means for study of intracellular biochemical changes.
 2. Proceeding from the fact that it has given quite uniform results in a fairly large healthy control group of persons and that different results are obtained in the cases of some clinically psychotic patients we may classify the test results of the first group as normal and of the second group as pathological.
 3. The test gives normal response in the cases of most of our patients diagnosed clinically as suffering from psychiatric conditions other than schizophrenia as well as in diabetics and hyperthyroid cases.
 4. Pathological test results are obtained chiefly within the schizophrenic range of diagnoses but some of the most clinically characteristic schizophrenics give normal results with this test.
 5. Present indications are that there is some factor present within the group of schizophrenic spectrum cases which is common to many of these cases but that the central group of well confirmed, long-term cases of schizophrenia is itself not positively distinguishable by this means.
 6. At the present state of the investigation the cases showing "normal type" enzymatic response can be tentatively characterized by the lack of the symptomatology of an acute psychotic attack of a sudden onset as it is typical in cases described as simple schizophrenia.
- (Authors' Abstr.)

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Semen Dyscrasia in Schizophrenia

Schizophrenics manifest many systemic disturbances of their physiologic functions.

The semen and its cytology are sensitive to general physiologic changes and are as deserving of study as any of the other body fluids.

The number of seminal analyses reported are too few to permit any conclusions as to either the genesis of schizophrenia or the etiology of spermatic monstrosities.

The results suggest the presence in schizophrenia of an X substance, which deranges spermatogenesis and produces the appearance of abnormal forms of spermatozoa.

(Author's Abstr.)

Stimulation of Suprabulbar Reticular Formation

Stimulation of the suprabulbar reticular formation produced a facilitation of flexor and extensor monosynaptic reflexes which was greatest during stimulation, which decreased markedly immediately after cessation of stimulation and then developed a late phase which persisted for two and a half to four and a half minutes.

The polysynaptic reflex evoked by stimulation of a skin nerve was inhibited, and the polysynaptic components of mixed-nerve-evoked reflexes were frequently inhibited by stimulation of points which caused facilitation of the monosynaptic reflex. In about 50 per cent. of the cases, however, the polysynaptic element of the mixed-nerve reflex was facilitated, but not to as great a degree as was the monosynaptic component.

Antidromic potentials obtained from the cord segment transmitting the testing reflex were facilitated by reticular formation stimulation.

Dorsal root reflexes and the intermediary element of the cord potential were suppressed by reticular formation stimulation which facilitated the monosynaptic reflex.

The late facilitation produced by stimulation of the reticular formation resembled in amplitude and duration the post-tetanic potentiation produced by stimulation of muscle afferents. These two types of facilitation summated when elicited simultaneously. The pre-synaptic effect of one (post-tetanic potentiation) conceivably summated with the postsynaptic effects of the other.

The decrease in latency of the monosynaptic reflex during the periods of facilitation produced by reticular formation stimulation was explainable by a decrease in excitation time, as shown by the orthodromic focal potential recorded from the motoneuron pool.

A production of oscillations or fluctuations in reflex spike height by reticular formation stimulation was observed, and its possible implication in relation to the problem of tremor was noted.

Stimulation of certain areas in the reticular formation produced a mixture of facilitatory and inhibitory effects, requiring more study.

Stimulation of the pyramid, unlike stimulation of the reticular formation, produced facilitation which lasted for only a brief interval after stimulation.

Recording potential difference between the central and the peripheral portion of a ventral root by means of a direct-coupled amplifier showed that depolarizing forces act upon the motoneuron pool during periods of facilitation.

Decerebration and decerebellation reduced the amplitude and duration of the late phase of facilitation following reticular formation stimulation.

It is possible that the late and prolonged phase of facilitation is due to prolonged discharge from the reticular formation. Conclusive evidence of this was not obtainable by the methods employed.

(Authors' Abstr.)

Validity of Rorschach Test as Measure of Psychological Effects of Brain Damage

In an experiment designed to investigate the validity of Rorschach test indications of brain damage and to explore further the intellectual and affective changes associated with brain damage, the Rorschach test was individually administered to 50 persons with proved brain damage or dysfunction and 50 matched controls with negative neurological and anamnestic findings. The subjects in the two groups were very closely matched in pairs on the basis of color, sex, chronological age, and years of formal education. In the brain-damaged group the cerebral lesions were heterogenous with respect to type, location, and extent. The control group included a substantial proportion of paraplegic and neurotic patients to minimize the possibility that intergroup differences might be attributed to hospitalization, chronic illness, and affective disorders.

The results indicated thorough-going suppression of mean values for the brain-damaged group on quantitatively scored Rorschach variables. In 18 of 21 instances, statistical comparisons indicated that the means for the brain-damaged group were significantly lower than those for the controls. The consistency with which the differences reached statistically significant levels suggested that brain damage causes a generalized suppression of personality factors.

Variables supposedly relating primarily to either intellectual or affective functions were significantly reduced. Evaluation of the frequency of occurrence of Rorschach test "signs" of brain damage indicated that they have some value in differentiating the groups. The brain-damaged patients tended to give less realistic associations, repeated responses without regard for form, often recognized the inadequacy of responses but were unable to improve or withdraw them, tended to give more concrete responses, were less able to define associations clearly, tended to withdraw from the problem and then reapproach it apparently in an effort to regain a new set, were less able in giving more than one association to a single stimulus complex, more frequently seemed to distrust their ability and sought help from the examiner, and sometimes engaged in overt catastrophic emotional reactions as their difficulty with the test situation mounted. The ability to identify reliably these indications of brain damage in an individual Rorschach protocol is dependent to a heavy extent upon the examiner's experience. In addition, it should be noted that differences in the occurrence of these signs between the group with and the group without brain damage seemed to appear only to a matter of degree. They do not constitute a basis for perfect discrimination even in the hands of an experienced examiner.

The same groups of patients were previously compared on Halstead's test of biological intelligence. The Halstead Impairment Index, as well as 8 of his 10 "discriminating" tests, yielded results which differentiated the groups at much more extreme confidence levels than were obtained with the Rorschach test. In spite of the considerably closer approach to perfect differentiation of the patients according to diagnosis obtained with Halstead's test, the availability and widespread use of the Rorschach test, together with the relatively encouraging results obtained, suggest the value of further investigation of the psychological effects of brain damage with this test.

(Author's Abstr.)

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Use of Large Doses of Cortisone in Schizophrenia

Nine nondeteriorated schizophrenic women were given 500 mg. of cortisone daily for from 4 to 10 weeks. These patients were studied intensively from the psychiatric, physical, and laboratory points of view.

1. Three patients showed slight and transient psychiatric improvement. Five were definitely made worse. One seemed unaffected. Many showed an increase in psychomotor activity.

2. No significant long-standing beneficial therapeutic results were obtained with use of cortisone alone. Cortisone did not appear to work synergistically with electroshock therapy.

3. Six patients revealed clinically demonstrable physical changes. Two showed a modified Cushing syndrome.

4. No significant alterations in electrolytes or other blood chemistry studies were seen. A significant eosinophile drop occurred in six patients. Two showed a significant drop in basal metabolic levels.

Several theoretical possibilities as to why all the patients did not show more pronounced evidence of hyperadrenalism are suggested.

(Authors' Abstr.)

Epinephrine-Mecholyl Test (Funkenstein Test)

Statistical study of 201 consecutive patients confirms the basic thesis proposed by Funkenstein and associates that prognostic implications can be derived from the epinephrine-Mecholyl test.

The recovery potential of the patients is shown to be positively correlated with the intensity of the autonomic response elicited. The recovery potential is high in patients with a greatly enhanced response to Mecholyl, either in cholinergic-muscarinic or in adrenergic-nicotinic direction, slightly less in patients with a moderately enhanced response, low in patients in whom one of the responses (that to epinephrine) is below par, and intermediate in those patients whose autonomic responses do not significantly differ from those of normals not under stress.

Absence of epinephrine-precipitable anxiety is prognostically favorable in cholinergic (muscarinic) overreactors, while presence of epinephrine-precipitable anxiety is prognostically favorable in the adrenergic (nicotinic) overreactors.

To electroshock therapy—of which a combined convulsive-nonconvulsive variant was employed similar to the combination of these modalities in electronarcosis—the most marked cholinergic and adrenergic overreactors responded best. Of the patients whose response to epinephrine was inadequate, none recovered with electroshock and/or psychotherapy, electroshock, as well as psychotherapy, being entirely ineffective in that group. The only Group V patients who achieved recovery were the two patients treated with insulin coma.

Epinephrine-precipitable anxiety nowhere represented a prognostically favorable item for response to electroshock therapy; however, it was less of a liability in our patients receiving combined convulsive-nonconvulsive treatment than in the patients treated with purely convulsive electroshock reported by Funkenstein and associates. In the combined Groups I-V, epinephrine-precipitable anxiety was thus eliminated as a liability altogether; the recovery rate of the patients with combined convulsive-nonconvulsive treatment (modified electronarcosis) was about equal for the subgroup with and for the subgroup without epinephrine-precipitable anxiety.

For Group IV, the recovery rate with psychotherapy was equal to that with electroshock therapy. Electroshock should therefore not be administered to Group IV patients except for purely symptomatic relief and should not be counted on to contribute to the ultimate recovery of the patient. This appears to depend upon the success of the psychotherapeutic work with the patient.

Epinephrine-precipitable anxiety is a prognostically favorable item for patients undergoing insulin therapy.

In the most favorable and the most unfavorable blood pressure reaction groups the predictive value of the epinephrine-Mecholyl test exceeds the predictive value of clinical diagnosis.

(Author's Abstr.)

Subcortical Connections from Temporal Cortex of Monkey

Connections from different parts of the temporal lobe to the basal ganglia, amygdala, and rhinencephalic cortex have been studied in the monkey by strychnine neuronography, evoked potential, and propagated seizure techniques. A preferential propagation was found from the temporal pole (TG) and from the superior temporal gyrus (TA) to the homolateral putamen, globus pallidus, amygdala, hippocampus proper, and hippocampal gyrus. Little or no propagation of activity to these structures was manifested upon stimulation of the second temporal gyrus (TE).

The findings indicate close functional relationships between the tip and the superior gyrus of the temporal lobe, and suggest a fundamentally different mode of organization of connections, and hence of function, of the second temporal gyrus.

Abundant and relatively direct connections from the tip and superior temporal gyrus to subcortical and rhinencephalic structures may help to clarify the role of these cortical areas in somatic, autonomic, and psychic spheres.

The facile propagation of seizure discharge initiated in the temporal tip and superior temporal gyrus to the amygdala may support recent proposals for an equivalent potentiality of both temporal cortex and amygdala in the genesis of psychomotor types of epilepsy. The present observation that evoked after-discharge is transmitted with equal facility to the putamen and globus pallidus raises the question of whether the basal ganglia, together with the amygdala, may participate in seizure activity during a psychomotor fit.

(Authors' Abstr.)

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Treatment of Multiple Sclerosis with Low-fat Diet

Five and one-half years' experience with a low-fat diet in the treatment of multiple sclerosis is summarized. This diet appears to lessen the severity of the disease by reducing the frequency and severity of the exacerbations. Its usefulness is greatest early in the disease, before significant disability and a steady progression of symptoms have developed. The period of observation has now been sufficiently long to give us some confidence in our observations, although we must not overlook the fact that since we are dealing with a disease having an average duration of perhaps 20 to 25 years, any conclusion concerning its therapy must still be tentative.

The mechanism by which the fat intake might influence the disease is discussed. Serious consideration is given to the hypothesis that patients with multiple sclerosis have a basic defect in the suspension stability of their blood, which is upset by the hyperlipemia following heavy fat meals.

(Author's Abstr.)

Antibrain Antibodies in Multiple Sclerosis

The complement fixation tests with the solutions of Folch-Lees proteolipides A, B and C, used as antigens, gave negative results.

The combined number of positive complement fixation tests with the multiple sclerosis brain antigens was 83.3 per cent. in multiple sclerosis patients.

The combined number of positive complement fixation tests in the control group was 42.6 per cent.

The difference between the number of positive complement fixation tests in multiple sclerosis sera and the number of those in normal sera was 40.7 per cent., a difference which is statistically valid.

The observation that the addition of normal sera to the positive multiple sclerosis sera reduces the positive reaction to a negative one, or to a much weaker one, led to a hypothesis that a substance is added capable of neutralizing the complement-fixing bodies, thereby liberating the complement.

This finding led to the selection of donors on the basis of this test for the treatment of the multiple sclerosis patients with blood transfusions.

(Author's Abstr.)

Intellectual and Affective Functions in Multiple Sclerosis

Widely divergent estimates have been reported regarding the incidence and extent of intellectual impairment in persons having multiple sclerosis. Some are based upon clinical impressions only; others are conclusions reached by the use of single psychological tests or batteries which have proved of inconsistent validity in organic brain damage. In the present study, an extensive series of tests was used; the results were analyzed statistically, and the findings were correlated.

Three groups of 13 patients each were used. One was composed of an unselected series of patients with multiple sclerosis; a control group consisted of patients with proved brain damage, and another control series was made up of patients having no history or evidence of damage to the brain. Each patient was matched with a corresponding one in the other groups on the basis of color, sex, age, number of years of formal education, and Wechsler-Bellevue full-scale Intelligence Quotient.

The Tests administered to each patient were the Minnesota Multiphasic Personality Inventory, Halstead's tests for measurement of biological intelligence, and the Rorschach Test. Halstead has presented evidence indicating that his battery measures aspects of intelligence which are particularly susceptible of impairment with brain damage, but are not closely correlated with I.Q. measures.

The profiles of all three groups were similar on the Minnesota Multiphasic Personality Inventory and were quite typical of neurotic disturbances. On the other hand, Halstead's battery indicated severe and parallel intellectual impairment in a high percentage of patients in both the multiple sclerosis group and the group with brain damage. The Rorschach Test indicated similar impairment, but of less striking magnitude. The findings in the group without damage to the brain, in contrast, were generally within the normal range.

Although the samples are small, the results indicate a statistically valid trend which warrants similar investigations of larger series.

(Authors' Abstr.)

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Variations in the Plasma Fibrinogen During the Course of Multiple Sclerosis

On the basis of Putnam's theory that the characteristic plaques in multiple sclerosis are caused by thrombi in the small veins of the central nervous system, investigations have been made with a view to demonstrating factors which might explain the origin of these thrombi.

A rise in the plasma fibrinogen has been demonstrated in multiple sclerosis; this is of special interest in this connection, as a raised fibrinogen content increases the agglutinability of the thrombocytes.

The investigations here described seem to indicate that variations of the plasma fibrinogen occur in multiple sclerosis, and that exacerbations of the disease are accompanied by rises in the plasma fibrinogen.

This gives rise to the question of what importance may be ascribed to the plasma fibrinogen in the case of thrombus formation in plaques. Several conditions, however, seem to go against a possible primary importance of fibrinogen in this process. Thus, often a raised fibrinogen occurred without clinical signs of the formation of new plaques. A raised plasma fibrinogen is, moreover, found in other chronic diseases without this giving rise to an increased frequency of thrombus formation. The periodically raised plasma fibrinogen content, as well as the clinically demonstrable exacerbations, is most likely to be an accompanying phenomenon to the actual cause of the disease.

(Author's Abstr.)

Effects of Diphenylhydantoin (Dilantin) on Adrenal Cortical Function

Diphenylhydantoin (Dilantin) was administered orally for varying periods of time to 12 nonepileptic human subjects and their adrenocortical activity was estimated by measurements of urinary excretion of 17-ketosteroids and corticoids. During acute administration of the drug 17-ketosteroid excretion remained essentially unchanged, but the corticoid excretion increased; during prolonged administration the excretion of both decreased significantly. These findings suggest that diphenylhydantoin may have an initial stimulatory and a later depressant action on the adrenal cortex. The implications of the results are discussed with regard to convulsive states in general and the mode of action of diphenylhydantoin as an anticonvulsant.

(Author's Abstr.)

Language Disturbances in Cerebral Disease

In summary, it is suggested that in arteriosclerotic dementia, and probably also in a certain proportion of epileptic cases, the striking decline in vocabulary level which is observed is related to the presence of localized cerebral lesions causing a mild aphasic state which may escape clinical detection by gross clinical observation but which manifests itself in a characteristic pattern of psychologic test performance. It is probable that this relationship also holds for other organic defect states. This possibility indicates that one must be extremely cautious in designating "typical" test performance patterns in cerebral disease, and it emphasizes the necessity for further investigations of homogeneous groups of patients. From the observations which have been reported it seems evident that the assumptions underlying the application of many so-called deterioration scales are in need of revision.

(Author's Abstr.)

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The Nature and Clinical Significance of Pigments in the Cerebrospinal Fluid

1. Oxyhaemoglobin, bilirubin and methaemoglobin are the pigments which commonly occur in coloured cerebrospinal fluid.

2. Oxyhaemoglobin appears at the onset of haemorrhage, progresses to a maximum the first few days and then gradually diminishes in amount. Bilirubin appears in two to three days

and increases in amount as oxyhaemoglobin decreases. Bilirubin persists for two to three weeks. Experiment *in vitro* suggested that only the action of living cells can produce bilirubin.

3. Methaemoglobin is found in fluids from subdural and intracerebral haematomas, craniopharyngiomas, and in fluids near encapsulated blood.

4. In cases in which there was obstruction to the flow of cerebrospinal fluid, cystic fluids and subdural effusions, the protein was elevated and bilirubin was the predominant pigment. The transudation of bilirubin complex from blood plasma is suggested in such situations.

5. In 10 of the 12 jaundiced patients, the spinal fluid was xanthochromic and bilirubin was the only pigment detected.

6. The benzidine, van den Bergh and potassium cyanide tests are useful simple confirmatory tests that can be performed in any ward laboratory when spectrophotometric methods are not available.

(Authors' Abstr.)

Neurological Deficiencies after Ablation of the Precentral Motor Area in Macaca Mulatta

These experiments were concerned with a reinvestigation of the function of the "motor" cortex studied in eight *Macaca mulatta*. Since the precentral motor area was defined as a functional unit that does not coincide with previous definitions of the "motor" cortex (Woolsey and Settlage, 1950; Woolsey *et al.*, 1952), this study was undertaken to determine the results of ablation of this area alone. The following conclusions were reached:

1. Precentral motor area lesions resulted in immediate severe voluntary impairment, hypotonia and diminished tendon reflexes in the extremities contralateral to the ablations; no ipsilateral deficits were observed.

2. Partial recovery of motor performance followed, and movements reappeared as soon at distal as at proximal joints; detectable impairments persisted at both.

3. Within two to twelve weeks the animals were able to pick up small stationary objects by apposition of thumb and index finger but after maximal recovery this manoeuvre was accomplished with only approximately half normal speed.

4. No significant spasticity developed. In the arms the triceps and finger jerks passed through a transient phase of moderate hyperactivity.

5. Placing and hopping reactions returned after one to three weeks in the affected limbs, but they were performed persistently in a retarded, hypermetric manner. The responses were enhanced with excitement of the animal.

6. The abdominal reflexes on the side contralateral to the lesion were diminished for four to six weeks following the operation, but after this interval they appeared as active as normal.

7. The plantar reflex consisted of apposition of all toes instead of the normal active flexion of the toes and frequent withdrawal of the entire hind-limb.

8. Atrophy of about 10 per cent. appeared in the limbs opposite the lesion during the period of greatest disuse and completely subsided after maximal recovery of motor function was achieved.

9. No grasp reflexes were obtained, although the lesions included Vogt's dorsal and part of the medial area 6aa.

10. These experiments do not support the concept that all parts of the motor cortex exert some control over all parts of the body musculature.

(Author's Abstr.)

Neurological Deficiencies Following Supplementary Motor Area Lesions in Macaca Mulatta

The supplementary motor area was defined by electrical stimulation as a distinct somatotopically organized field (Woolsey *et al.*, 1950, 1952), and this investigation was undertaken to determine the neurological deficits produced by its removal. The results were derived from lesions restricted to the supplementary area and from ablations involving either the precentral or supplementary motor area with injury to the other area. Experiments were also performed to determine if extirpation of the portions of the histologically mapped "area 6" not included in the precentral motor area would demonstrate motor impairment. The results are as follows:

1. The supplementary motor is a bilateral functioning system, for greater deficits were obtained after simultaneous bilateral than after unilateral ablations.

2. Unilateral supplementary area lesions produced weak, transient grasp reflexes in the contralateral limbs, and within one week moderate bilateral hypertonia of the shoulders. No noticeable paresis was present.

3. Simultaneous bilateral supplementary area ablations yielded practically no paresis, but posture and tonus were disturbed. Immediately there was increased resistance to passive movements of the limbs, and during an interval from two to four weeks contractures supervened. The hypertonia was encountered in the flexor muscles. The tendon reflexes were hyperactive within a day to two weeks with some of them (finger and toe jerks) becoming clonic. The spasticity demonstrated topographical localization according to the portions of the areas removed. Grasp reflexes were present for three to five weeks.

4. When the supplementary area was removed bilaterally in two stages with over six months intervening between the operations, only slight increased resistance was located at the ankles. No hyperactive tendon reflexes appeared, and weak, temporary grasp reflexes were

observed after the second operation. This indicates that practically no release phenomena will follow the second operation provided a sufficient time interval intervenes between two such operations.

5. If no addition to a simultaneous bilateral supplementary lesion there occurred unilateral injury of the precentral hind-limb area, the immediate resistance and final contractures were less in the lower limb opposite the additional precentral ablation.

6. If with removal of the precentral motor area the supplementary area was damaged, there resulted localized increased resistance to passive movement according to the portions of the area encroached upon. This was true with unilateral and bilateral ablations.

7. The lesion involving unilateral precentral plus supplementary limb areas resulted in immediate hypotonic paresis and impairment of tendon reflexes. This stage of diminished reflex activity within two weeks merged into a state of increased reflex activity; the hypotonus changed to moderate increased resistance to passive movements in the fore-limb and to approximately normal tonus in the hind-limb. The experiment defined the supplementary motor area as concerned with controlling movement, for the paralysis observed was greater than after unilateral precentral motor removals.

8. The placing and hopping reactions persistently disappeared in the affected extremities following unilateral precentral plus supplementary lesions; but previous simultaneous or later removal of the limb area of the precentral or of the supplementary motor system in the opposite hemisphere permitted the reactions to be performed crudely in the affected extremity.

9. Ablation of "area 6" not included in the precentral or supplementary motor area resulted in no motor impairment of the limbs, no grasp reflex, and no hypertonia. This indicates that the only motor functional parts of "area 6" are those portions included in the precentral and supplementary motor area.

(Author's Abstr.)

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Complications of Chlorpromazine Treatment

Chlorpromazine deserves acceptance as a new form of psychiatric treatment.

To be really effective in schizophrenia it must be given in much larger doses than other investigators have considered safe.

There are many complications to chlorpromazine therapy. None appears to be dangerous and all may be managed satisfactorily by reduction of dosage or temporary withdrawal.

(Author's Abstr.)

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Oral Metrazol Therapy in Senility

Fifteen senile patients nearly all of them disorientated, confused, often restless, untidy and quarrelsome, received oral Metrazol therapy. Generally, 2 tablets of 1½ grains each were given 3 to 4 times a day. Twelve of the 15 patients were definitely improved even after so short

a time as 4 to 5 weeks. Usually demonstrable improvement occurred within 10-14 days after the therapy was started. Although 2 patients became definitely more alert mentally—one of them even requesting to go home and later discharged in his own cognizance. All the other 10 men became more amenable to ward care, so that restraint frequently could be dispensed with and the constant aimless wandering about the ward ceased.

What can be achieved with Metrazol therapy in mentally less confused cases remains to be seen. Judging from the results so far, Metrazol therapy certainly is of value to reduce the nursing difficulties inherent in the care of such senile cases. This in itself is no mean advantage which enables the personnel to give more time to those other patients who require special attention.

(Authors' Abstr.)

Clinical Comparison of Raudixin and Rau-sed in Chronic Mental Illness

Raudixin and Rau-sed were given to fifteen chronically disturbed mental patients. The clinical responses to either drug, in relation to hyperactivity, overtalkativeness, assaultiveness, destructiveness, agitation and tension were the same. There was no significant difference in decreases of blood pressure occasioned by either medication.

The authors feel that these drugs can be used with a marked degree of safety and that chronic mental patients may obtain considerable benefit from this treatment.

(Author's Abstr.)

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Hippocampal Seizure States in Guinea Pig

1. The electrical activity of hippocampus and isocortex in unanesthetized guinea pigs during resting state and in response to external stimulation is described. It is shown that there is a differential response of hippocampal and isocortical activity to complex environment stimuli.

2. Mechanical and electrical stimulation of the hippocampus induce local and propagated seizure discharges at relatively lower thresholds than stimulation of isocortex, striatum and thalamus.

3. The structure of the hippocampal seizure discharge as analyzed from combined ink-writer and cathode-ray oscillograph recordings is a composite of several activities of different frequency orders with relatively constant mutual phase relationships. In particular, the clonic stage is characterized by slow pulses of 0.3 to 5 c/sec., with superimposed waves of 10-30 c/sec., carrying on top of them brief spikes of 2.5 msec. duration. Each of these complex pulses is preceded by a shower of 100-200 c/sec. spikes. Periods of apparent silence are characterized by a deviation of the basis potential from the isoelectric line, of opposite polarity to the one exhibited during the clonic pulse. Gross spikes and spike-and-waves appearing at the onset of a "tonic-clonic" after-discharge are rarely observed in the hippocampus but are common in the epileptic activity of neocortex, striatum, amygdala and thalamus.

4. Hippocampal after-discharges spread widely over cortical and subcortical structures, as well as over the cerebellum. They show a preferential spread over the centrocaudal isocortex, often avoiding the rostral neocortex.

5. Unless unduly strong stimulation, resulting in a grand mal convulsion, is applied, there are only slight changes of behavior concurrent with the after-discharge: arrest of ongoing behavioral activity and decrease of reflex responses.

6. These various findings suggest that the hippocampus may play an important role in epilepsy in general. This structure may participate in, and may indeed initiate the manifestation of those forms of epilepsy which are chiefly characterized by disturbances of awareness and mental confusion.

(Authors' Abstr.)

Electrophysiological Studies on the Connections of the Amygdaloid Nucleus in the Cat. Part I: The Neuronal Organization of the Amygdaloid Projection System

1. The subcortical and cortical connections of the amygdaloid complex are studied in 23 cats using the technique of recording evoked potentials to single shock and repetitive electrical stimulation of the amygdala.

2. The subcortical projection area of both baso-lateral and cortico-medial subdivision of the amygdala overlap widely. This subcortical projection field extends from the septum and the base of the head of the caudate nucleus back to the tegmentum mesencephali comprising essentially beside the just named structures the preoptic area, the hypothalamus, the subthalamus, the entopeduncular nucleus and some nuclei of the diffuse thalamic projection system.

3. Short latency responses on baso-lateral amygdaloid stimulation, most probably mediated directly without synaptic interruption, are found in the "primary projection field", which covers the basal part of the telencephalon medium and the adjacent rostro-basal pole of the diencephalon. From here responses are relayed to the remainder of the projection area—the "secondary projection field"—through short multisynaptic neuronal links. This "secondary projection field" comprises mainly the more caudal parts of the centro-basal core of gray matter extending from the hypothalamus to the tegmentum mesencephali. This latter area may eventually be activated through a more direct amygdalo-mesencephalic system by-passing the hypothalamus.

Short latency responses from the cortico-medial group extend further caudal into the hypothalamus than those observed on baso-lateral amygdaloid stimulation. It seems therefore that the "primary projection field" of the cortico-medial amygdaloid subdivision is more extensive. On the other hand no evidence is found for a tegmental projection of this nuclear subdivision.

4. Pathways from the baso-lateral nuclear group to their "primary projection field" in the subcortex do not run through the stria terminalis. This fiber bundle originates in the cortico-medial part of the amygdala and represents the main outflowing fiber path of this amygdaloid subdivision. The baso-lateral part uses shorter and more direct pathways to its "primary" subcortical projection area. However, there are intraamygdaloid association fibers through which over multi-synaptic relays the baso-lateral nuclei may discharge through the stria terminalis also.

5. The cortical projection area of the amygdala comprises neocortical, paleocortical and archicortical structures. The neocortical areas in connection with the amygdala are homologous with the anterior temporal and insular region in man.

Multisynaptic chains exist from the amygdala *via* the paleocortex of the piriform lobe to the archicortex of the hippocampus, which although very responsive to amygdaloid stimulation does not receive any direct fiber connection from the amygdala. The possibility of a recurrent firing of the hippocampus from the amygdala *via* the septum and ascending fornix fibers is also briefly discussed.

6. The fibers originating in the amygdala seem to belong mainly to the group of thinly myelinated and unmyelinated elements. Some of the properties of the amygdaloid projection system are best explained on the assumption that part of the neurones at least are comparable to autonomic elements of the C-fiber group.

7. The functional significance of the experimental data are briefly discussed. The wide variety of amygdaloid stimulation effects as observed by several authors becomes understandable in view of the data presented in this study, since they show that excitation originating in the amygdala impinges upon a wide subcortical area known to contain the central representations of various integrative mechanisms regulating somatic, autonomic, behavioral and electrographic activities.

8. The cortical projection pattern of the amygdala corroborates clinical electroencephalographic and electrocorticographic findings in cases of temporal lobe epilepsy with ictal automatism, where activation of epileptogenic activity in the anterior and mesial temporal as well as in the insular cortex is observed presumably from a primary source in the amygdaloid region.

(Author's Abstr.)

Electrophysiological Studies on the Connection of the Amygdaloid Nucleus in the Cat. Part II. The Electrophysiological Properties of the Amygdaloid Projection System.

1. The changes in excitability within the amygdaloid projection system were studied using the method of single shock and repetitive stimulation of the amygdala. As a routine the following technique was applied: first, the responses to 1 c/sec. single shock responses were observed and then the changes this response underwent during 10 c/sec. or 50 c/sec. repetitive stimulation were studied. At the end of the period of repetitive stimulation single shock stimulation at 1 c/sec. was immediately resumed in order to obtain information about facilitatory or inhibitory after-effects.

2. With this technique the following changes were observed: recruitment or obliteration during repetitive stimulation, often followed by potentiation in the post-tetanic single shock stimulation phase. Changes in latency—either decrease or increase—were seen to go along with these changes in excitability in many instances.

3. Recruitment was very often observed with 10 c/sec. repetitive stimulation. It was absent with 50 c/sec. stimulation. Recruitment was most prominent with long latency responses suggesting multisynaptic transmission and therefore was considered as an amplification process due to building up of a facilitatory state at successive synaptic stations.

The opposite process of building up of inhibitory phenomena leading to progressive obliteration of the response was occasionally seen also, though less frequently.

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An Experimental Study of Pathways from the Basal Ganglia

Lesions were placed in the basal ganglia in three specimens of *Macaca mulatta*. The animals were observed during a survival period of from two to 8 weeks. The brains were studied in Marchi preparations. The following results were obtained:

1. The origin of the ansa lenticularis is not confined to the medial division of the globus pallidus. Additional possible sources are the lateral division of the globus pallidus and the putamen. The tract may be joined by fibers from the temporal and insular cortex.
2. Fibers from the basal ganglia were followed into various areas of the dorsal and the ventral thalamus and the hypothalamus and into the red nucleus of the mesencephalon.
3. The origin of the lateral cortico-habenular tract is basal to the globus pallidus, presumably in the amygdala and the pyriform lobe cortex.
4. Small electrolytic lesions in the globus pallidus result in no detectable abnormalities in behavior in the macaque.
5. A lesion destroying the globus pallidus unilaterally and interrupting the fibers basal to the globus pallidus bilaterally produces a marked reduction in the monkey's willingness to move. Peculiar jerks occurred whenever this monkey was touched.

(Author's Abstr.)

The Inferior Olive. A Golgi Study

Detailed study of the inferior olive in a large group of animal and human brain stems, using the silver chromate impregnation method of Golgi, has revealed new information regarding the structure of this nucleus.

1. The cell population of the inferior olive is not homogenous in structure. Cells with large, simple and relatively unramified dendrite patterns occupy the caudal portions of the dorsal and medial accessory nuclei. Cells with smaller, highly ramified, spherical dendrite arbors of the type described by Ramon y Cajal are found in the rostral portions of the accessory nuclei and the phylogenetically newer primary olivary nucleus.

2. In preparations of human inferior olive, a large cell with very extensive dendrite distribution has been found in the center of the olivary grey matter.

3. In addition to the classical afferent arborizations, at least two new patterns of axon terminations have been described.

(a) The majority of fibers from the descending tract which enter the rostral pole of the olive terminate in simple bifurcating fibers bearing either small nodules or clusters of terminal buttons. Small numbers of fine fibers with similar patterns of termination enter the olive from the region of the white matter near the midline.

(b) Fibers of larger caliber enter the dorsomedial aspect of the nucleus and terminate on olive cell somata or on orange-staining bodies in clusters of terminal buttons or in more complex rosette forms. It is suggested that these fibers fractionate the olive cell pool by manipulating firing thresholds on the basis of impulse patterns from centers of higher integration. The question is raised whether this "feedback" type of circuit might not represent part of the basic pattern of the so-called relay nucleus.

4. A small number of efferent axons have been seen to leave the rostral pole of the olive and course cephalad.

5. The olivary neurophil is described in detail. Anatomical and functional evidence is presented which suggests that the olive may be especially adapted, through the configuration of its neuropil, to maintain a low threshold to afferent impulses.

6. Within the neuropil, many small nodules and oval bodies are seen, lying apparently free, or in contact with axonal or dendritic processes. The nature and function of these bodies is unknown.

7. Spherical, orange-staining bodies with rims of unstained refractile substance are described throughout the olive and in other parts of the nervous system. Many of the rosettes of the heavy afferent fibers appear to terminate on these bodies, which also make contact with various elements of the axonal and dendritic neuropil and with what are presumed to be astrocyte processes. The possible nature of these bodies is discussed and evidence is brought forward which indicates that they may belong to the group of oligodendroglia. If so, recent studies indicating the close relationship of neuroglia to acetylcholine esterase suggest that orange-staining body-neural relationships may furnish the anatomical substrate for one type of neurohumeral interaction in the central nervous system.

(Authors' Abstr.)

APRIL

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Histochemical Studies of Glycogen of the Area Postrema and the Allied Structures of the Mammalian Brain

The area postrema and other paraventricular structures were studied, with the histochemical methods for glycogen, in the mouse, rat, hamster, guinea pig, rabbit, cat, dog, and man. The brains, after prompt excision from the animals, were fixed in Rossman's fluid, followed by embedding in paraffin. The sections were stained with the lead tetraacetate-Schiff method or the McManus method.

The area postrema and intercolumnar tubercle are provided with abundant sinusoidal blood vessels surrounded by conspicuous connective tissues, which are moderately positive but saliva-resistant, a reaction attributable to the presence of mucopolysaccharide.

The area postrema of all animals examined, excepting man, reveals the presence of variable amounts of glycogen granules. The most evident deposit was in the rabbit and hamster, the intermediate in the dog, pig and cat, and the least in the mouse, rat and guinea pig. The guinea pig shows, however, a prominent accumulation of glycogen in the outskirts of this area. The glycogen particles are observed to be mainly located either around the blood vessels or on the intercellular fibrillar structures.

A moderate deposition of glycogen is demonstrated within the ependymal cells and adjacent neuropil of the supraoptic crest in the mouse and rat, while none is found in the hamster. The elongated ependymal cells of the subcommissural organ contain a moderate amount of glycogen in the mouse, rat and hamster. The intercolumnar tubercle shows a small amount of glycogen in the hamster.

(Author's Abstr.)

Organization of the Cerebral Cortex. III. A Study of Aging in the Human Cerebral Cortex

The quantitative changes in cell number with increasing age were investigated according to the method of Bok. Sections of cortex were removed from a human series extending from birth to 95 years.

The counting of cortical cells and rank correlation of cell number with age indicate that the greatest decrease in cell number with increasing age occurred in the superior temporal gyrus followed by the precentral gyrus and then the area striata. The postcentral gyrus showed the least change in cell number. It was noted that, at least between the newborn and 16 to 21 year old group, the decrease in cell number was an apparent rather than a real decrease. The factors responsible for this were discussed. In the precentral gyrus, a differentiation of the cortical layers was observed from the superior to the inferior extent of the gyrus. The portion closest to the lateral fissure reveals a stratification. The superior portion is not delineated in this way.

Whereas all the cortical layers show a decrease in cell number with age, external and internal granular layers are particularly affected. The dominant cell type in these layers in the newborn is the granule cell. In the older age groups these layers contain more small pyramidal cells than granule cells.

(Author's Abstr.)

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The Association of Dementia with Radiologically Demonstrated Cerebral Atrophy

In routine clinical practice at least 85 per cent. of 68 cases of unexplained dementia in later life showed evidence of cerebral atrophy in the A.E.G.

In 213 A.E.G.s performed in the investigation of cases without dementia 11 per cent. showed an unexplained cerebral atrophy, and these were most commonly associated with epilepsy of late onset.

Features of the A.E.G. that suggest an associated dementia are cortical sulci greater than 0.5 cm., air trapped in the insular region, and enlargement of the lateral ventricles particularly marked in the region of the trigone.

(Author's Abstr.)

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Examination of the Sensory System in Patients After Hemispherectomy

Following hemispherectomy these patients seemed to experience only a minimal reduction in their sensory perception. The reason the loss is relatively minimal after excision of cerebral areas generally considered necessary for the recognition and discrimination of stimuli is not entirely established. The thalamus unquestionably acts as the primary, and probably major, receptive center for perception of pain, temperature, and light touch stimuli. These modalities of sensation remained nearly intact after hemispherectomy. Finer discriminative powers are lost to some extent but not entirely. Tests for stereognosis are only minimally less accurately completed on the involved than on the uninvolved side. This is believed due to the assumption by the remaining (and since early childhood the dominant) hemisphere of these functions usually carried out by the contralateral sensory areas. Nielson has alluded to this assumption of function by his statement that aphasia does not develop in infants from a unilateral lesion regardless of laterality. Similarly, patients with destruction of the internal capsule by vascular lesions (producing anatomically a lesion comparable to a hemispherectomy) retain no such sensory perceptive powers as do these patients with hemispherectomies. An alternative possibility is that in the thalamus there is an ability to discriminate stimuli on a spatial basis. Such localization has been demonstrated in macaques. However, the cortex undoubtedly functions to delineate better such tactile stimuli. It is emphasized that in the interpretation of these data it must not be forgotten that the patients in this series were handicapped pre-operatively and had been so handicapped for many years. It is believed that because of this fact transference of these data to patients without long standing pre-existing neurologic functional loss cannot be done.

(Authors' Abstr.)

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The Hypothalamic Syndrome in Rats with Experimental Lesions

Lesions were placed in the hypothalami of Sprague-Dawley rats by means of electrodes inserted perpendicular to the midsagittal plane of the brain. Some with low colonic temperatures died of starvation. Others (15 rats) exhibited hyperphagia, polydipsia, obesity and sham rage; none of these showed changes in colonic temperatures. The female rats in which the estrus cycles were studied showed disturbances of the cycle.

The lesions responsible for obesity were bilaterally symmetrical, either filiform, umbonate, spindle-shaped, or cylindrical, sometimes bridging the third ventricle, in the anterior portion of the ventrotuberal hypothalamus. Large and extensive lesions of the anterior hypothalamus were usually necessary to produce the obese condition or changes in estrus cycles; small lesions in this area failed to produce these conditions. Midtuberal lesions of the hypothalamus need not be large. It was found that thread-like lesions, provided they damage part of the ventromedial nuclei and the areas immediately lateral to these nuclei, were sufficient to produce the obese condition without changes in estrus cycles or colonic temperatures.

(Author's Abstr.)

Ballism Associated with Partial Destruction of the Subthalamic Nucleus of Luys
A case of ballism occurring in a 72 year old hypertensive male controlled after ventro-lateral cordotomy was reported clinically and pathologically. Death resulted from broncho-pneumonia 23 days after onset of the dyskinesia. Sections of the brain were studied by the Marchi method. The lesion, destroying approximately 31 per cent. of the right subthalamic nucleus, was located in the lateral half of the nucleus rostrally and in the dorsal half of the nucleus caudally. No definite conclusion regarding somatotopical localization within the subthalamic nucleus could be drawn from this case.

- The following conclusions were drawn:
1. The limit of physiologic safety for the human subthalamic nucleus is of the same order as in the rhesus monkey despite its absolute size, being approximately 15 times as large (relative size is about the same).
 2. Pre-existing striatal deficit contralateral to a lesion of the subthalamic nucleus appar-ently does not prevent the appearance of ballism in man.
 3. The primary blood supply of the subthalamic nucleus is probably derived from branches of the posterior cerebral artery.
 4. The possibility that localized lesions of the spinal cord may abolish ballistic activity without producing signs of symptoms of pyramidal deficit is suggested by the case reported here. An attempt to confirm this result would seem worthwhile.

(Author's Abstr.)

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Chlorpromazine in the Management of Acute Alcoholic States

Experience with chlorpromazine hydrochloride in 164 alcoholic patients is reported.

In relatively large doses this drug possesses properties that make it extremely helpful in the management of acute alcoholic states. It produces immediate control of motor excitement and of nausea and vomiting, permits a restful, relaxed sleep, and contributes to the relief of tension and anxiety. The patient is able to retain fluids and nourishment, can be readily aroused for appropriate nursing care, and thus is quickly able to return to a state of physiological normalcy.

No addiction to the drug has been noted. There are few unpleasant side effects. During initial therapy, orthostatic hypotension of moderate degree is fairly common. Occasionally the hypotension may be severe. Thus, the blood pressure of patients treated with chlorpromazine should be closely followed, particularly when large doses are given, and the patients should be kept in a recumbent position.

(Authors' Abstr.)

1. Biochemistry, Physiology, Pathology, etc.

Formation of Ammonia in Brain Tissue and Adenylic Acid Deaminase. Tsukada, Yasuzo and Takagaki, Genkichiro. [Kagaku (Science), 24, 572 (1954).]

When tissue homogenates from guinea pig brain were incubated at 37° and pH 7.0, rapid increase of NH₃ and concomitant decrease of glutamic acid (I) were observed. The amount of NH₃ formed was fully accounted for by the decrease of (I). With longer incubation periods adenine derivatives were deaminated to form inosine derivatives, but the deamination was not observed with brain slices; therefore adenylic acid deaminase was considered to be inactive in slices, showing a difference from the enzyme system in a homogenate. Amination of inosinic acid to adenylic acid did not occur in brain slices even in the presence of inosinetriphosphate (ITP) and glutamine. Addition of (ITP), however, increased formation of NH₃ even in brain slices. The effect of (ITP) may be due to activation of glutaminase, rather than to amination of inosine derivatives.

T. KOBAYASHI (Chem. Abstr.)

The State of Cholesterol and Phospholipides in the Brain Tissues of Animals. Nedzvetskii, S. V., and Ratnitskaya, S. S. [Biokhimiya, 19, 677 (1954).]

Blood vessels and dura of cattle brains were removed. Tissues were ground with glass in 0.9 per cent. NaCl and centrifuged. The supernatant was designated as extract 1 and the sediment subjected to a second similar extraction and centrifugation. The second supernatant was designated as extract 2. The sediment was then extracted twice with 7 per cent. NaCl and residue ground in 0.25 per cent. NaOH. Extractions thus obtained which gave the biuret reaction were tested for content of cholesterol and phospholipides. Tests were also made to determine whether the cholesterol and phospholipides are in combination with the proteins of the brain tissues. It was shown that by the NaCl solvents 24-27 per cent. of the cholesterol is

extracted from the gray matter of the brain, 6-8 per cent. from the white matter, and 11-18 per cent. from the cerebellum. In these extractions the cholesterol is in combination with the brain proteins. By the same processes 33-45 per cent. of the phospholipides are extracted from the gray matter, 27-33 per cent. from the white matter, and 36-45 per cent. from the cerebellum. About 50 per cent. of the phospholipides thus extracted are not in union with the proteins, or united in only a weak manner. The 0.25 per cent. aqueous solution of NaOH extracts the remainder of the cholesterol and phospholipides which are in combination with the brain tissue proteins. These are easily precipitated by HCl and again redissolved by NaOH without any change in their original complex-structure.

B. S. LEVINE (Chem. Abstr.)

The Thiamine Dehydrogenase Content of the Nervous System. Titaev, A. A. [*Biokhimiya*, **19**, 645 (1954).]

In the nervous system of invertebrates, thiamine dehydrogenase (TD) is more active than in the brain of vertebrates. (TD) is evenly distributed over all parts of the brain of the fish. In the brains of mammals, including man, (TD) is concentrated mostly in the posterior part of the hypothalamus; in vertebrates the highest concentration is found in the hypophysis. There is a gradual diminution of (TD) concentration in the brain of vertebrates from fishes to mammals, especially in the anterior part of the brain. It is completely absent in the cortex of the brain hemispheres at the higher stages of evolutionary development of vertebrates. In the embryo (TD) is found in approximately the same concentration in the hemispheres as in other parts of the brain. One of the reasons for the high activity of (TD) in the nervous system of invertebrates (and plants) is the presence of polyphenol oxidase, which hastens the (TD) reaction as a result of adrenaline oxidation. It is suggested that a close connection exists between the function of the (TD) system and the vegetative part of the nervous system.

B. S. LEVINE (Chem. Abstr.)

Influence of Bicarbonate Ions on the Glycolysis of Brain Suspensions. Keller, Herbert. [*Hoppe-Seyler's Z. physiol. Chem.*, **299**, 93 (1955).]

Under aerobic conditions HCO_3^- accelerated lactate formation and reversed its retardation by adenosinetriphosphate. Under anaerobic conditions the effect of HCO_3^- was smaller. The inhibitory action of creatine phosphate on lactate formation was augmented by HCO_3^- .

ERICH HEFTMANN (Chem. Abstr.)

The Ionic Permeability of Nerve Membranes. Keynes, R. D. [*Recent Develop. Cell Physiol., Proc. 7th Symposium Colston Research Soc. Univ. Bristol*, 43-9, (1954).]

A review of current concepts and the evidence therefore of the part played by ion movements in the conduction of the nerve impulse and the relation between nerve function and metabolism.

J. A. BAIN (Chem. Abstr.)

Beriberi Toxin. 1. Matusda, Shin. [*Vitamins (Japan)*, **5**, 207 (1952).]

When chicks were bred on diets deficient in thiamine, beriberi toxin appeared in the plasma, and by the injection of this plasma to chicks bred on the low-thiamine diets, these chicks contracted beriberi. It was assumed from the histological studies that this toxin was the abnormal metabolite produced in viscera owing to the beriberi disease.

HIROYASU FUKUBA (Chem. Abstr.)

Cortical and Cerebral Convulsions Caused by Bile and Bile Salts. Takeda, Tatsuo. [*J. Physiol. Soc., Japan*, **16**, 747 (1954).]

Bile of cow, dog, cat and toad produced cerebral clonic convulsions in rats. Among the bile salts, deoxycholate and warmed trihydroxycholate caused clonic convulsions, while 3-hydroxy-7-ketocholate induced clonic and tonic convulsions. Although cholic acid alone showed no effect, it could suddenly become active by addition of butyric acid.

ITIRO TYUMA (Chem. Abstr.)

Iodine Content of the Central Nervous System of Cats After Thyroidectomy. Tutaev, G. V., and Isichenko, N. A. [*Byull. Eksptl. Biol. i Med.*, **32**, No. 9, 38 (1954).]

Iodine content of the central nervous system was determined at various periods following operation. Control tests were run on normal animals and showed the distribution of (I) in the different areas of the brains in descending order: cortex, cerebellum, pons, and medulla oblongata; 5-7 days following the operation the (I) decreases in the following increasing order: cortex, cerebellum, pons, and medulla oblongata; 15-20 days later the level of (I) is unchanged in medulla oblongata, higher in cortex and pons, and lower in cerebellum; 30-50 days later the largest amount of (I) is found in pons and medulla oblongata, the least in cerebellum and cortex. After 60-120 days the largest amount is found in cortex. Thus the cortex, despite its depleted (I) content, retains its leading position among the four brain areas.

A. S. MIRKIN (Chem. Abstr.)

Behavior of Some Phosphate Esters in Brains at the Start of Convulsions Induced by Fluorocitrate and Fluoroacetate. Dawson, R. M. C., and Peters, R. A. [*Biochim. et Biophys. Acta*, **76**, 254 (1955).]

Young rats were administered fluoroacetate (I) intraperitoneally or fluorocitrate intracerebrally and phosphate esters and citrate were determined in the brain, kidney and heart at the start of convulsions. Marked changes were not observed in the levels of 10 min.-labile P. Small, significant decreases were noted in the cerebral levels of phosphocreatine and labile nucleotide P in animals administered (I). Citrate levels increased. The experiments showed no evidence that convulsive discharge in (I) poisoning can be initiated by a lack of water-soluble energy-rich P esters in the brain but the possibility of localized depletion was not excluded.

MORTON PADER (Chem. Abstr.)

Importance of the Determination of Citric Acid of Cerebrospinal Fluid in Various Affections of the Nervous System in Children. Crisalli, Mary and Capra, Carlo. [*Minerva pediatrica*, **6**, 424 (1954).]

In 12 normal children (8 months-11 years), the citric acid (I) content of the cerebrospinal fluid averaged 2 mg. per cent. (I) (for a total of 58 patients with acute, chronic and degenerative diseases of the nervous system) was very high in tuberculous meningitis, inversely proportional to the glucose content, high in serous meningitis and poliomyelitis, and higher the more evolutive the process in progressive degenerative encephalitis and in cases of tumor.

C. SCANDURA (Chem. Abstr.)

Behavior of the Glucose Contents of Blood and Cerebrospinal Fluid After Sugar Administration to Patients with Hydrocephalus. Gueli, U., et al. [*Riv. pediatrica siciliana*, **8**, 1 (1953).]

In 6 of 8 children with hydrocephalus, the (basally lower) blood glucose curve (I) after the administration of 4 g. glucose/kg. body weight was like that of healthy controls; that of the (basally higher) cerebrospinal fluid glucose had a behavior opposite to (I) and was different from controls.

C. SCANDURA (Chem. Abstr.)

The Iodine Content of the Central Nervous System and Thyroid Gland of the Hypophysectomized Cats. Tutaeve, G. V., and Isichenko, N. A. [*Byull. Eksptl. Biol. i Med.*, **38**, No. 10, 42 (1954).]

After hypophysectomy the (I) content of the brains of the animals which were operated on was 61.7 μ /100 g. while that of normal animals was 265.6. On the other hand, the (I) content of the thyroid gland increased as compared with that of normal animals. However, this increase is found only after a long period following the operation. The first few days it is decreased. Despite the eventual increase of the (I) content of the thyroid gland that of the brain remains low which emphasizes the very important role played by the hypophysis in the metabolism of (I) in the central nervous system.

A. S. MIRKIN (Chem. Abstr.)

Phospholipide Fractions in Multiple Sclerosis and Normal Serum. Bernsohn, Joseph and Namajuska, Izolina. [*Proc. Soc. Exptl. Biol. Med.*, **88**, 124 (1955).]

Determinations on normal serum for cephalin, lecithin and sphingomyelin by the methods described gave values of 9.4 per cent., 6.5 per cent. and 19.7 per cent., respectively, of the total phospholipides. In serums of multiple sclerosis patients the distribution was similar, although the total phospholipide content of the serum was a little below normal.

L. E. GILSON (Chem. Abstr.)

Carbohydrate Metabolism in Brain Disease. IV. Effect of hydrocortisone and corticotropin (ACTH) on the Metabolic Effects of Administered Glucose in Patients with Chronic Schizophrenic and Manic-depressive Psychoses. Henneman, Dorothy H. [*Arch. Internal Med.*, **95**, 241 (1955).]

The changes in the blood concentration of glucose and of lactic, pyruvic, citric, and α -ketoglutaric acids after the administration of glucose were studied in patients with chronic psychoses. The changes induced by the administration of corticotropin or hydrocortisone prior to the administration of glucose suggest that these hormones inhibit the metabolic pathways whereby pyruvate and lactate enter the tricarboxylic acid cycle and potentiate the pathways whereby citrate is utilized.

EDWARD J. VAN LOON (Chem. Abstr.)

Relation Between Age and Cholinesterase Activity in Several Rabbit Brain Areas. Aprison, M. H., and Himwich, H. E. [*Am. J. Physiol.*, **179**, 502 (1954).]

The cholinesterase (ChE) activities were determined in the frontal cortex, caudate nucleus, superior colliculus, and medulla oblongata of the growing rabbit brain. All (ChE) activities were low during gestation and rose to maximal values at different periods after birth. First the medulla oblongata increased to a maximum at 15 days and following an early rapid fall stabilized at an intermediate value. The superior colliculus was the next to attain a maximum at approximately 8-9 months after which there was a slow decrease during the rest of the time interval studied. The caudate nucleus and frontal cortex were the last to reach a maximum at approximately 18 months.

E. D. WALTER (Chem. Abstr.)

Effect of Adrenocorticotropin on Some Aspects of Brain Metabolism and Electroencephalogram. Torda, Clara. [Congr. intern. biochim., Résumés, communs., 2^e Congr., Paris, 65 (1952).]

The data of 2 other papers are summarized and discussed. The increased electrical activity of the brain after administration of adrenocorticotropin is relatively independent of changes in blood circulation and in concentration of Na and K. It is probably due to increased NH_3 in the brain.

W. C. TOBIE (Chem. Abstr.)

Enzyme Concentrations in the Brain and Adjustive Behavior Patterns. Krech, David, et al. [Science, 120, 994 (1954).]

Rats were grouped according to spatial or visual preference on the basis of their performance in a standardized insoluble maze. The animals were later killed, and tissue was taken from their visual (I), somesthetic (II), and motor areas (controls) and analyzed for their cholinesterase (ChE) content. It was found that ChE was 20 per cent. lower in (I) than in (II) ($P=0.001$). The spatial group showed a significantly higher (ChE) content than the visual group. The visual group showed a progressive and statistically significant increase in ChE activity from (I) through (II) to the motor area.

J. D. TAYLOR (Chem. Abstr.)

Distribution of Substance P and Choline Acetylase in the Brain. Zetler, Gerhard and Schlosser, Lucie. [Naunyn-Schmiedeberg's Arch. exptl. Pathol. Pharmacol., 224, 159 (1955).]

Eleven areas in each of 10 brains from cattle were investigated for substance P and 22 different areas in 10 human brains. The highest concentration was found in the substantia nigra, the second highest in the ala cinerea. The presence of enteramine can erroneously cause a high reading for substance P. This was avoided by the use of the isolated guinea pig ileum by Gaddum's method. Since in the investigation for choline acetylase in human brains autolytic processes interfere, the effect of autolysis was determined with rat brains as test substance. Autolysis caused in every instance a decrease in choline acetylase activity. The localization of choline acetylase was investigated in human and dog brains. Areas with high choline acetylase contained little substance P and vice versa. This is not caused by an inhibition of choline acetylase by substance P since there is no interference if both are mixed. Substance P occurs chiefly in areas with a small content of cholinergic neurons.

A. E. MEYER (Chem. Abstr.)

Effects of the So-called Emotional Stimulation of an Animal on the Functional State of the Thyroid Gland. Amiragova, M. G. [Doklady Akad. Nauk. S.S.S.R., 99, 325 (1954).]

Emotional stimulation of experimental animals (dogs) leads to repression of the ability of the thyroid to accept iodine from the surrounding medium; this state of the thyroid becomes normal after 4 hours following the stimulation. Cats gave a similar response. Emotional stimulation increases the secretion of thyroid products into the blood. The determinations were made by detection of radioiodine, I^{131} , which was introduced per os or intraperitoneally. The emotional stimulation was produced by teasing a cat with a dog and vice versa.

G. M. KOSOLAPOFF (Chem. Abstr.)

Inositol in Brain Metabolism. Kerken, H., and Maibauer, D. [Klin. Wochschr., 32, 1113 (1954).]

The inositol (I) content of brain, sympathetic ganglia, liver, pancreas, thyroid, adrenal, and kidney were determined microbiologically. The (I) content of cerebrospinal fluid is 3 times as high as that of serum, and brain tissue has an active (I) metabolism.

E. HEFTMANN (Chem. Abstr.)

Influence of the Hypothalamus on the Blood Lipides. Inoue, K., et al. [Med. J. Osaka Univ., 5, 475 (1954).]

When the ventromedial hypothalamic nucleus of the rabbit was stimulated electrically, the total cholesterol of rabbit serum decreased 6-28 per cent. at about 60 minutes, and the lipide P and total lipide decreased in about half of the animals. When the lateral nucleus was stimulated, these values were unchanged or increased. 42 references.

A. DIETZ (Chem. Abstr.)

Inhibitory Effect of Malonate on the Respiration of Brain Tissue with Special Reference to the Potassium Effect. Kimura, Y., and Niwa, T. [Nature, 171, 881 (1953).]

Guinea pig brain cortex slices respiring in Krebs-Ringer-phosphate solution in the presence of 0.1 M KCl are acutely susceptible to malonate (10^{-3}M) as contrasted with normal respiration which is quite resistant to malonate. The possibility is suggested that in KCl-saline solution, either the Krebs cycle is the main pathway of brain tissue respiration or the Krebs cycle, which is masked in some way or other under normal conditions, is opened up and brought into operation by the addition of excess K.

J. D. T. (Chem. Abstr.)

Integration of the Bioelectric Activity of the Brain in Relation to Compensating Oscillograms in Man. Schminke, G. A. [Byull. Eksptl. Biol. i Med., 38, No. 11, 71 (1954).]

B. S. L. (Chem. Abstr.)

2. Pharmacology and Treatment

Laboratory and Clinical Observations on Chlorpromazine (SKF-2601-A)—Hemodynamic and Toxicological Studies. Moyer, J. H., et al. [*Am. J. Med. Sci.*, **227**, 283 (1954).]

In laboratory studies on dogs, chlorpromazine (I) was a hypotensive agent decreasing peripheral resistance with a variable effect on cardiac output, and no evidence of acute renal toxicity or renal hemodynamic alterations. When injected into dogs it appeared to increase Na and water excretion. In clinical studies, the only suggestive evidence of toxicity consisted of alterations of the electrocardiograms of 2 seriously ill patients. The more intensive response to (I) that was noticed in patients with hepatic disease suggests that biotransformation of (I) may occur in the liver.

MARION HORN PESKIN (Chem. Abstr.)

Action of Camphor on the Synapses in the Motor and Autonomic System. Rohr, H. [*Naunyn-Schmiedeberg's Arch. exptl. Pathol. Pharmacol.*, **224**, 327 (1955).]

Experiments on frogs and mammals showed that the paralytic effect of camphor is not based on a curare-like action at the neuromuscular synapses. Experiments with the isolated perfused frog heart with stimulation of the vagal area showed on application of camphor, of the antagonistic system camphor-dihydroergotamine, and of camphor-prostigmine that the inhibition of the vagus by camphor is only an apparent vagus paralysis. Concentrations of camphor, efficacious on the frog heart, cause in dogs, cats, and rabbits convulsions. Lower doses influence the vagus stimulation only if afferent vagus condition is preserved.

A. E. MEYER (Chem. Abstr.)

The Blood Brain Barrier—the Effect of Acidic Dissociation Constant on the Permeation of Certain Sulfonamides into the Brain. Goldsworthy, Patrick D., et al. [*J. Cellular Comp. Physiol.*, **44**, 519 (1954).]

In mature, male rats, 1 hour after intraperitoneal injection, those sulfonamides with pK_a values below 8 gave a brain to blood concentration ratio of approximately 0.1. The ratios increased to 0.36–1.0 through the range of pK_a 8 to 10.5 and then decreased as pK_a increased. There was no correlation between molecule weight or lipid solubility of the sulfonamides and their distribution.

H. L. MASON (Chem. Abstr.)

Factors Involved in Drug-produced Model Psychoses. Fisher, R. [*Experientia*, **10**, 435 (1954) (in English).]

There is a close inverse correlation between the single dose required to produce psychoses and the affinity for wool for mescaline-HCl, Methedrine-HCl, methanol tartrate of lysergic acid monoethylamide, and methanol tartrate of lysergic acid diethylamide.

D. S. FARNER (Chem. Abstr.)

Changes of Behavior and Electroencephalogram in Rhesus Monkeys Caused by Chlorpromazine. Das, N. N., et al. [*Arch. intern. pharmacodynamie*, **99**, 451 (1954).]

Chlorpromazine injected into monkeys produced striking behavior changes, so that fierce animals became somnolent and showed almost complete akinesia. The electroencephalograms were characterized by high voltage, slow electric activity over the whole cortex. Probably the drug suppresses the action of the awakening "upward discharge" of the ascending reticular formation.

M. L. C. BERNHEIM (Chem. Abstr.)

Pharmacological Properties and Application of the New Drug Pachycarpin. Mashkovskii, M. D., and Kryshova, N. A. [*Sovet. Med.*, 1953, No. 2, 36–8; *Referat. Zhur. Khim.*, 1954, No. 20290.]

Pachycarpin (I) inhibits conduction transfer of nervous stimulation through the vegetative ganglia, stimulates contraction of the uterus, intensifies protective-inhibitory processes in the cerebral cortex, and possesses low toxicity. (I) is also effective in some cases of arterial and muscular disorders as well as in sympathetic ganglion disorders. Limits of the medical application of (I) are indicated.

E. WIERBICKI (Chem. Abstr.)

Chlorpromazine as a Therapeutic Agent in Clinical Medicine. Moyer, John, et al. [*Arch. Internal Med.*, **95**, 202 (1955).]

Chlorpromazine is an effective inhibitor of psychomotor excitement and agitation and appears to have some anticonvulsant activity. It is also an effective anti-emetic agent.

EDWARD J. VAN LOON (Chem. Abstr.)

Effect of Chlorpromazine on the Electric Activity of the Cerveau Isolé. Das, N. N., et al. [Naunyn-Schmiedeberg's Arch. exptl. Pathol. Pharmacol., **224**, 248 (1955).]

Mesencephalic transection (cerveau isolé) of the brain stem was carried out in cats at the collicular level and the electric waves were taken from the surface of the frontal and occipital lobes of the cortex. Doses of 0.2–0.5 mg./kg. chlorpromazine caused marked changes in the electrocorticogram of the thalamo-cortical system. The spindles and slow waves, characteristic for the preparation disappeared a few minutes after the injection. In some experiments there appeared temporarily spikes and waves.

A. E. MEYER (Chem. Abstr.)

Treatment of Epilepsy with Cation Exchangers. Mertens, H. G., et al. [Klin. Wochschr., **33**, 35 (1955).]

Withdrawal of Na by feeding of cation-exchange resins has favorable clinical results in epilepsy.

ERICH HEFTMANN (Chem. Abstr.)

Applicability of Dormiphen for Sleep Therapy from the Pharmacological Point of View. Sobek, Vojtech. [Casopis Lekarů Ceských, **93**, 532 (1954).]

Among the narcotics studied, Amytal Na (I) and Dormiphen (cyclohexenyl-ethylbarbituric acid) (II) were more toxic than Bromisoval (III) and Evipan (IV) in mice (LD_{50} 0.27 for (I) and 0.32 g./kg. for (II)). Chronic toxicity tests showed no significant differences. The hypnotic activity of (III) and (IV) is less than that of (I) and (II). There was no remarkable difference between (I) and (II) as far as the influence on blood pressure, body temperature, and glycemic curve was concerned. The activity of (II) decreased during long-term administration. (II) can be substituted by (I) for the purposes of sleep therapy, (II) can be used as an adjuvant.

IVO M. HAIS (Chem. Abstr.)



[Photograph by Howard Coster

JOHN DUNNE

[Frontispiece